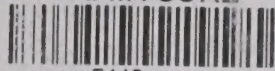


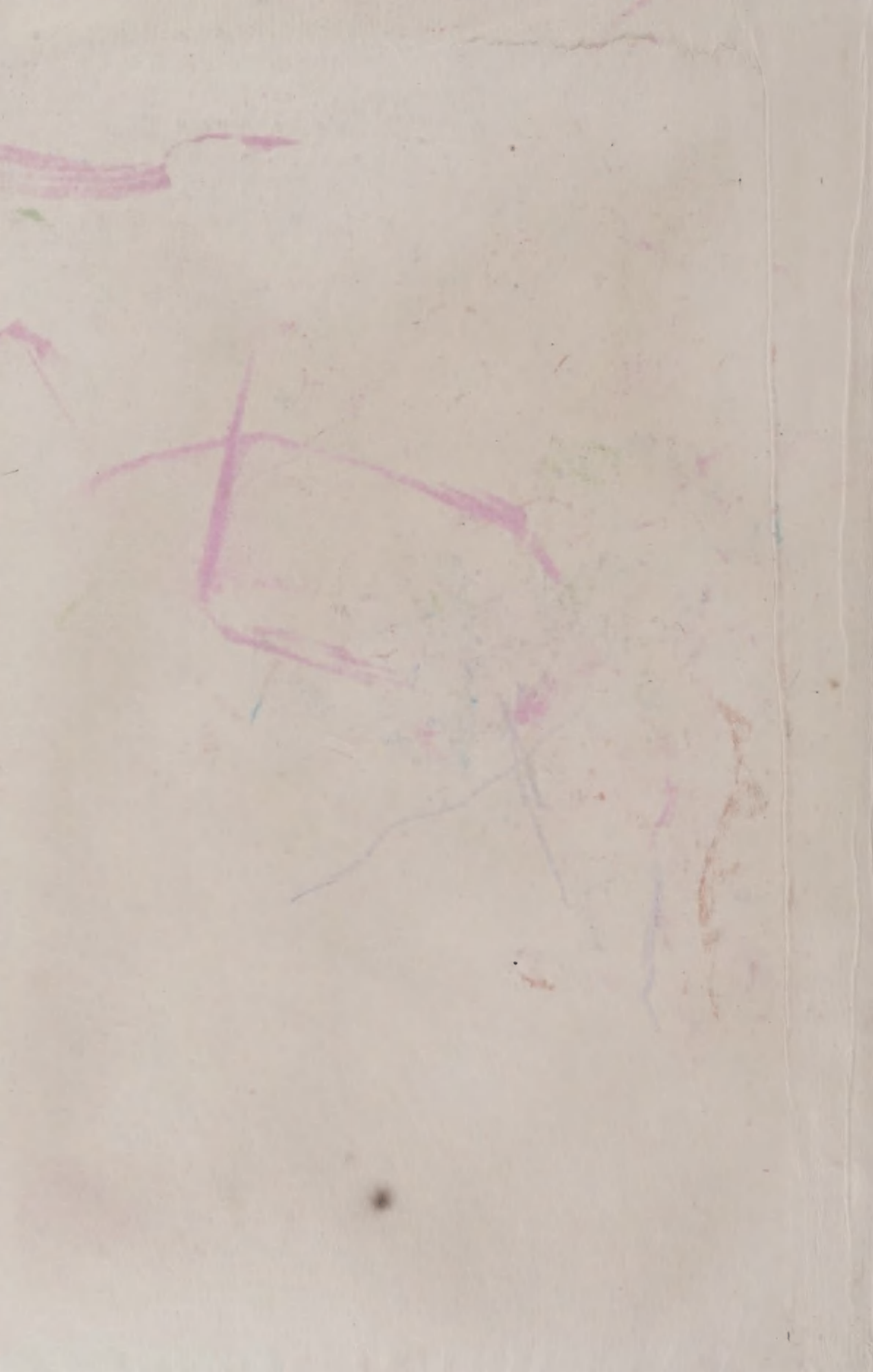
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# INDUSTRIAL TOXICOLOGY

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# INDUSTRIAL TOXICOLOGY

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*Scientist Director, Ret.,  
United States Public Health Service*

SECOND EDITION



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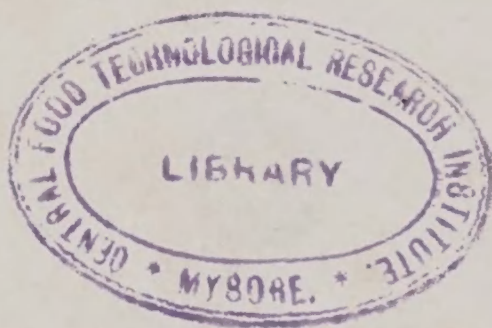
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## PREFACE TO THE SECOND EDITION

Advantage has been taken of the demand for a second edition of this book, not only to make several minor changes, but also to write a number of new sections and to introduce new material in order to bring the book thoroughly up to date. The great advances in chemical technology, the manufacture in large quantities of new chemical substances, and the increasing accumulation of toxicological data have collectively imposed an obligation to contribute further information on those new substances which have received substantial toxicological investigation.

It is a great pleasure to express my thanks to my colleagues here and abroad who, by sending me reprints of their scientific papers, have greatly eased the burden of library search. I wish to record especially my appreciation and gratitude to many friends and associates who have rendered me most valuable aid with material, assistance, and suggestions. Acknowledgment is also made to publications of the U.S. Tariff Commission, the Manufacturing Chemists Association, and the U.S. Bureau of Mines for use of certain data.

It is to be hoped that the inclusion of the various tables in the Appendix will increase the usefulness of the book.



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## INTRODUCTION

In an earlier period of our industrial development workmen were exposed to smoke, dust, fumes, and gases without regard to the possible injurious nature of many of these substances. Certain occupations, such as the mining of mercury, were formerly notorious in this respect. Furthermore, this condition was recognized in only very few instances and exposure to fumes or dusts of a deleterious type was generally recognized as a somewhat disagreeable and accepted condition of many occupations. The fact that some workers in mines, mills, or factories sickened, were forced to leave their occupation, and later died, did not always bring with it the realization that the nature of their work was a factor. In some occupations where industrial disease was prevalent there were often individuals who had been immersed in such an environment most of their working life and yet remained apparently strong and healthy. Such cases would be cited as indicating the general harmlessness of their occupation and those who sickened were regarded as weaklings. Many industrial diseases, such as phosphorus poisoning, were undetected for years, or, as in the case of manganese poisoning, were undetected for generations. The scrutiny of occupation as a factor in disease, although emphasized long ago by Ramazzini, is a comparatively modern development. Industrial physicians only a generation ago were largely concerned with the more external factors of employment—hernia, lumbago, cataracts in the case of glass workers, deafness in boiler-makers—or in incidental disease, such as ankylostomiasis among miners or tuberculosis among cotton spinners. The latter were, of course, related to poor sanitation and poor nutrition, respectively, and were by no means peculiar to the occupation of the worker.

Knowledge, however, of the existence of occupational disease became more and more evident and, although locally confined at first, gradually spread. Thus, such terms as "grinder's rot", "phossy jaw", "painter's colic", "chrome itch", and "miner's phthisis"

gradually appeared in industry and in the literature. Within the past generation industrial physicians have been alerted to the danger of much of the smoke, dust, or gases to which workers were exposed, scientists have actively investigated the effects of many of these aerial contaminants on animal life, and engineers have instituted control measures in industry to reduce the hazard of exposure.

Poisoning familiarly occurs as the result of ingestion of toxic substances and this doubtless influenced much of the earlier industrial hygiene thought. As a result, stringent sanitary measures were advocated and adopted in certain industrial processes in order to prevent possible entrance of industrial poisons by mouth. These precautionary measures included such matters as a complete change of clothing on entering a shift, careful scrubbing of the hands and face before eating lunch, and a thorough washing and shower at the end of the work period. While excellent in themselves, these measures do not include the sanitation of breathing and instances of industrial poisoning have occurred where workers had observed strict cleanliness yet were exposed to dangerous concentrations of dust, fumes, or gases. Inhalation is now recognized as one of the most dangerous routes of entrance of industrial poisons.

### Gases, Fumes, and Dust

While the greater part of industrial smoke consists largely of carbon and is relatively harmless, it frequently contains gases which are dangerous if continuously breathed or if breathed in high concentration and, in addition, it may contain noxious fumes or toxic dusts from certain processes.

From the point of view of industrial hygiene a gas may be considered to be any aeriform or completely elastic fluid which does not become liquid or solid at ordinary temperatures. Fumes or vapors consist of material in the near-gaseous, or extremely fine particulate form which condense to liquids or solids at room temperature. Dusts,



on the other hand, consist of larger particulate matter suspended in air. It must be realized that these definitions are not rigid and that they merely indicate somewhat roughly different stages of attenuation of matter. It is possible, for instance, to have mercury dust suspended in the air of a workroom, due to constant attrition of mercury spilled on the floor and carried into the air as extremely minute droplets following mechanical agitation. At the same time, mercury fume may be present as the result of heating this substance and finally the vapor tension of mercury is such that true, gaseous mercury may also be present to a slight extent. It is important for the industrial hygienist to keep these distinctions in mind. The detection and estimation of mercury gas in air by means of the photoelectric mercury detector depends upon the absorption of ultraviolet light of a wave length of 2537 Å and the degree of absorption is a measure of the amount of *gaseous* mercury present. However, this instrument would not indicate the total mercury present in an atmosphere where particulate mercury or dust from any of its compounds was also present.

While dusts have been classified as particles or aggregates of particles of from 150 microns to 1 micron in diameter, fumes of from 1 micron to 0.2 micron in size, and smokes as particles less than 0.3 micron in diameter, size alone represents at best only a rough separation of these three classes. The mode of formation must also be considered. Thus, dusts ordinarily result from mechanical attrition and distribution, while fumes and smokes are formed and carried into the air usually as the result of chemical reaction or the sudden dispersion of a chemically active substance by release of pressure or by explosion.

The disperse systems, or aerosols, in which the dispersion medium is a gas, differ from other disperse systems in the great disparity that exists between the density and structure of the disperse phase and the dispersion medium. The mere fact that two such disperse systems contain amicroscopic particles similar in magnitude does not necessarily mean that the properties of the two

systems are identical, although they may have many points of similarity. In the case of dust, a great deal of work is required in order to reduce a solid to fine dust, *i.e.*, to overcome the forces of cohesion that originally held the particles together in addition to the work required in distributing the particles throughout the dispersing medium. Even though a certain degree of uniformity finally is attained by settling or other means, dispersed dust of the finest order of magnitude is less uniform in structure than aerosols produced by the condensation of vapor. These factors have some weight in devising means of sampling and analysis of aerial contaminants.

The evaluation of aerial contaminants is very frequently a matter of importance to the industrial hygienist and a knowledge of the properties of such disperse systems as those indicated above, as well as the properties of gases and vapors in relatively low concentrations, is of particular value with reference to the analytical detection and determination of the constituent contaminants.

The composition of the aerial contaminant to which workmen in a given plant are exposed is of course of paramount importance to the industrial hygienist. This is usually known, or information may be obtainable from the management. In some cases, however, an unknown or unsuspected factor may be present and careful investigation may be necessary before the culprit is revealed. Cases have occurred, for example, where arsenic, cadmium, or selenium existing as unsuspected impurities in the material being fabricated have caused illness and death. An unrecognized by-product of manufacture may cause difficulty, or a change in the formula of basic material used in manufacture may bring about an unhygienic situation. The industrial hygienist is required not only to ferret out the occupational disease hazard but also—very necessarily—to know its characteristics, a proper method of sampling, and the most reliable method of analytical evaluation in terms of air content. His study includes the weighted or average exposure of employees at various stations and occupations. Furthermore, he



is required to know something regarding the toxicity of the aerial contaminant in order to define the conditions under which employees are to be permitted to work in such an environment.

The toxic effects of many hazardous materials in industry are well known and it is comparatively easy to define safe working concentrations. There exist many substances in common use in industry, however, which are toxicologically not well defined. Unfortunately, toxicity cannot be evaluated with the ease with which a chemical constant, such as a boiling point, melting point, or index of refraction, may be determined. Even with arduous investigation extending over many months, the toxicologist can at best give only a very general answer regarding the poisonous nature of a given substance. It would be of inestimable benefit of course, if one could—knowing the composition and molecular structure of such a substance—predict its physiological properties.

### Chemical Constitution and Physiological Response

The possibility of relating chemical constitution and physiological activity has long proved a fascinating field of speculation. The advantages of defining the toxicity of a substance from its constitution or structural formula are, as indicated above, obvious. Unfortunately, however, the matter is not simple. Certain relations exist, it is true, between structure and toxicity. For instance, ethyl and methyl alcohol, although differing in one important respect, are very similar in many of their other physiological properties, and propyl, butyl, and amyl alcohols might be assumed to act similarly. These latter alcohols do, in fact, resemble the lower members but with a progressive increase in toxicity. An analogous increasing toxicity might therefore be anticipated in the higher members of the alcohol series. This reasoning, however, is nullified by the changing physical properties of the higher members. In spite of a similar chemical structure, the higher alcohols become increasingly insoluble in body fluids and as a result there is an overall decreasing toxicity beyond a certain point. A similar increase in toxicity with an

increasing number of carbon atoms is noted with sodium acetate, propionate, butyrate, and valerianate. Many other such relationships have been pointed out as more toxicological information has become available.

The replacement of a hydrogen atom with chlorine in the saturated hydrocarbons results in an immediate change in toxicity; the entrance of such a halogen group in the organic sulfur compounds greatly intensifies the toxicity of the resulting compound. When one chlorine group is introduced into ethyl sulfide, which is a weak poison, the resulting monochloroethyl sulfide is found to be markedly toxic, while the introduction of a second chlorine atom results in dichlorodiethyl sulfide, or mustard gas, which is a very strong poison indeed. However, no such general rule can be applied in other cases. The successive replacement of hydrogens by chlorine in the methane molecule, which of itself is not toxic but merely an asphyxiant, results in monochloromethane,  $\text{CH}_3\text{Cl}$ , dichloromethane,  $\text{CH}_2\text{Cl}_2$ , trichloromethane,  $\text{CHCl}_3$ , and tetrachloromethane,  $\text{CCl}_4$ , respectively. These substances, however, do not follow a pattern of increasing toxicity. For instance, chloroform with its excellent narcotic properties, as well as the attendant possibilities of liver and heart damage, is less toxic in general than carbon tetrachloride on the one hand and much less toxic than methyl chloride on the other hand. Yet dichloromethane, which occupies an intermediate position, is far less toxic than any of the other members of this group. It does not follow therefore that there is any direct correlation between the number of chloro groups and the toxicity.

The relatively inert and inoffensive hydroxyl group when introduced into an organic molecule frequently results in an increase in toxicity. Thus, methanol,  $\text{CH}_3\text{OH}$ , has pronounced toxic properties compared with the parent substance and monohydroxybenzene,  $\text{C}_6\text{H}_5\text{OH}$ , or phenol, has marked poisonous properties over and above those of benzene. Increasing the number of hydroxyl groups may also increase the toxicity of the aromatics. For example, the introduction of a second hydroxyl group in the benzene ring yields resorcinol,  $\text{C}_6\text{H}_4(\text{OH})_2$ ,

which is more toxic than phenol, while the introduction of a third group yields pyrogallol, which is the most toxic of the three.

The entrance of an alkyl group into the molecule of a substance may also intensify its poisonous quality. Dimethyl resorcinol,  $C_6H_4(OCH_3)_2$ , is more toxic than resorcinol,  $C_6H_4(OH)_2$ . On the other hand, an alkyl group may diminish the toxic effect in other substances. Dichloromethyl arsine,  $As(CH_3)Cl_2$ , is very toxic, while the introduction of a second methyl group, as in dimethyl chloroarsine,  $As(CH_3)_2Cl$ , yields a substance of weaker toxicity.

While the introduction of a chlorine group in aliphatic hydrocarbons increases the toxicity in general, this is not necessarily true in the case of the aromatic hydrocarbons. Thus, monochlorobenzene is less toxic than benzene itself and has been of no particular significance as an industrial poison.

It appears to be a general rule that *iso* compounds are somewhat less toxic than normal compounds. *iso*Propyl alcohol has a somewhat lower toxicity rating than normal propyl alcohol; *isobutyl* alcohol than normal butyl alcohol. A most interesting difference in toxicity has been found to exist in the benzene hexachlorides which have recently received attention as insecticides. In this case, the gamma derivative of 1,2,3,4,5,6 hexachlorocyclohexane,  $C_6H_6Cl_6$ , has been found to be especially lethal in action compared with the other four known isomers (1). Woodard and Hagan (2) found the gamma isomer to be as much as 60 times as toxic for certain warmblooded animals as other isomers of benzene hexachloride. In the case of many other optically isomeric substances, great differences may also be found in toxicities. For instance, 1-hyoscyamine is twice as active physiologically as dl-hyoscyamine (atropine) and moreover the laevo compound is 12 to 20 times as active as the dextro compound (3). Usually, but not invariably, the laevo compounds are more active than dextro compounds. Thus, Cushny found 1-hyoscyamine to be 16 to 18 times as active as d-hyoscyamine and twice as active as dl-hyoscyamine. Similarly 1-adrenaline was 12 to 15 times as active as d-adrenaline in its

vasoconstrictor action and twice as active as dl-adrenaline. On the basis of rather indirect evidence, it is possible that the difference in physiological behavior of such stereoisomers is due to the ability of one or the other to combine with some protein or other constituent of the cell. However, sufficient quantitative data are not available to define clearly the mechanism of physiological activity and stereochemical configuration. The problem of relating chemical constitution and physiological action is even more confusing when it is recalled that substances of diverse chemical nature may produce similar physiological effects. The aliphatic narcotics, for example, include a large variety of structural type, such as hydrocarbons, alcohols, ethers, amines, and sulfones. According to Ing (4), these substances appear to achieve their effect by modifying the physicochemical conditions of the cells due to certain physical properties shared by all classes of these compounds and not by the presence of certain pharmacodynamic groups.

It will be apparent therefore that while the temptation to rationalize regarding the prediction of toxicities may be great, the evaluation of toxicities of new substances is fraught with considerable uncertainty. Since no great rational scheme is available to aid, except rather sketchily, in deciding upon the toxicity of a given substance, it is inevitably necessary to carry out experimental work with animals.

### Experimental Toxicology

Experimental industrial toxicology does not differ widely from that of experimental pharmacology, since they both use the resources of chemistry, physics, physiology, and pathology to achieve their purpose. However, the pharmacologist is primarily interested in therapy rather than toxicity. Furthermore, he is interested in the effects of administration of a substance by mouth, or by intravenous or subcutaneous injection and rarely in the effects of inhalation, except in the case of inhalation anesthetics. The refinements of approach to certain physiological reactions adopted by the pharmacologist, however, often yield data of fundamental importance within a relatively short



space of time. The toxicologist on the other hand may be compelled to follow an intricate procedure which is arduous and time consuming in order to define a given physiological response. Moreover, toxicological studies frequently depend upon pathological changes following the administration of small amounts of such toxic materials as gases, fumes, or dusts and these changes usually occur very slowly.

Toxicological investigations are in general based upon animal experimentation for human experimentation is, of course, indefensible. It is true that animal experiments provide only indirect evidence of the probable action of toxic substances on man, yet they are nonetheless of the greatest value. They not only afford information regarding upper toxic limits, but by long-continued study, reveal changes in lower concentrations which are of the greatest importance. In experimental work of this character, a considerable amount of interpolation is necessary and evaluation of the experimental results requires both acumen and careful judgment. Moreover, there are many poisons which produce completely different effects in different species of animals. Mice and guinea pigs, for example, are more sensitive to poisoning by trichloroethylene (acetylene trichloride) than cats, while rabbits are less sensitive than cats. On the other hand, cats are more sensitive to lead poisoning than dogs and the latter more so than rats. Although such qualitative and quantitative differences may exist, nevertheless there can be no doubt that animal experiments are of value since they give an indication of the type of toxic action, as well as the relative toxicity of the substance under investigation.

The great advantage of animal experimentation is, first of all, the control of dosage and secondly, the degree to which poisoning can be carried. This yields most useful information in tracing similar effects in humans accidentally poisoned and in warning against human exposure beyond a certain degree.

Although the effects of exposure by inhalation are of paramount importance, animal studies also usually include other forms

of administration, such as ingestion, intravenous injection, intraperitoneal injection, and subcutaneous injection. The latter form of administration is perhaps the least used as absorption is frequently slow and has less significance than the other forms. Intravenous injection provokes the most immediate response and is often useful in studying the immediate effects of substances upon the hemopoietic system. Intraperitoneal injection is one means of following the slow absorption of relatively insoluble substances, but is of particular value in studying the physiological response of various substances. For instance, when pure silica suspensions are intraperitoneally injected, a reaction occurs which is typical and fairly constant (5). Sayers and Miller found three types of reaction occurred with various dusts—absorptive, inert, and proliferative. The absorptive reaction occurs when fine dusts, such as calcite, limestone, gypsum, and cement, are injected. After sufficient time, this material disappears from the peritoneal cavity without the formation of any scar tissue. In the case of the inert reaction, the dust remains distributed about the peritoneum by the action of phagocytes, sometimes forming flat nodules, which do not tend to progress or form fibrous scar tissue. Soapstone, carborundum, and coal dusts exhibit this inert reaction. In the proliferative reaction, nodules form which continue to increase in size with the formation of fibrous or scar tissue. Quartz, chert, and flint dust produce this reaction. These three types of reaction correspond very closely with the results obtained by the inhalation technique. While this method perhaps requires further exploration, it is useful in the approximate classification of dusts.

The inhalation technique with reference to dusts, fumes, and gases is by far the most useful method used in experimental toxicology. In the case of gases, the various concentrations to which animals are exposed may be regulated with accuracy. Hence, the exposure may be clearly and accurately defined. With fumes and dusts, the concentration of fume or dust in the air may be determined by exact chemical analysis. Whether or not the animals always breathe

in the amount in the atmosphere may not be so accurately defined in many cases as small animals, such as guinea pigs, tend to huddle together and may be able to filter out some of the dust or fume to which they are exposed.

For the purpose of exposure, gas-tight or dust-tight exposure chambers of large size are usually used and animal cages may be placed directly in the exposure chamber. The gas may be introduced in known amounts and rapidly distributed throughout the exposure chamber by means of small fans. Substances which are sufficiently volatile, such as solvents, may be introduced in known amount into a constant current of air and the breathing concentration may be accurately calculated. In addition, of course, samples of the exposure atmosphere may be taken in most cases and analyzed chemically.

Fumes, such as metal fumes, may be generated by arcing between electrodes of the metal carrying 110 a.c. current and an appropriate resistance. In order to prevent the formation of metallic oxide fume, it is usually necessary to generate this fume in an atmosphere of inert gas, such as nitrogen or helium, and "bleed" it into an incoming air current. Oxide fumes are readily formed by arcing in air or in an atmosphere of oxygen. Fumes of many organic substances may be formed by heating the material to the volatilization temperature in the incoming air stream.

Dusts must be suspended in air in very finely divided form in order that they may remain in suspension as long as possible and so that the material is of sufficient degree of fineness to be carried deeply into the animals' lungs. An elutriating device is useful for this purpose (6), since it permits a constant flow of very finely divided dust of more or less uniform size. In the case of dust exposures, it is difficult to control the amount of dust in the exposure atmosphere and hence it is necessary to draw small samples from time to time for analysis. Even though the dust concentration is accurately known, the amount carried into the animals' lungs is questionable, as a variable amount is removed by the filtering action of the nose,

part of the dust remaining in suspension is removed before the air enters deeply into the lungs. The ciliated epithelium found throughout the extent of the air-passages and their prolongations constantly sweeps out air-borne particles and only the very finest material penetrates to the lung alveoli.

The evaluation of exposure and the localization of toxic material in the various animal tissues, and the determination of its excretion metabolites, are of course dependent upon exact analytical procedures. Toxicological analysis frequently involves the isolation, identification, and determination of quite minute amounts of poison. In cases of metal poisoning the application of emission spectrography is of invaluable assistance. With organic substances, especially when only minute amounts may be isolated and purified, identification may prove more difficult. Indeed the original poison may have become metabolized so that it may no longer be identifiable, and above all the metabolic fate or the nature of its breakdown products may be unknown. However, where this field has been sufficiently explored the determination of the end-products of metabolism has been of great value. Thus, it is possible to trace benzene poisoning by the urinary excretion of phenol and conjugated ethereal sulfates, picric acid by the urinary excretion of 4,6-dinitro-2-aminophenol, methanol by formic acid and formaldehyde, acrylonitrile by thiocyanate excretion and trichloroethylene by the urinary excretion of trichloroacetic acid.

Modern methods of detection and identification have enormously facilitated this type of investigation. Just as emission spectrography in the ultraviolet region has proved of great value with reference to inorganic substances, absorption spectrophotometry both in the ultraviolet and the infrared regions has been a most valuable tool in the hands of the analyst with reference to structure as well as identification and determination of toxic substances. The development of chromatography and the availability of radioactive tracers have also served to facilitate analytical investigation. X-ray diffraction technique presents a particularly useful means of identification, and



the more recent type of equipment registers the position and intensity of radiation graphically, so that more rapid examination is possible. X-ray diffraction analysis not only has the great advantage of identification, but requires only a very small amount of substance. Moreover, this substance is not destroyed or changed in any way. Furthermore, as with spectrography, a visual record is obtained. The electron microscope has proved useful for the analysis of airborne particulates and in the investigation of the role played by quartz particles in initiating fibrotic changes in the lungs.

Those who are interested in the field of toxicological analysis will find the publications of Fabre (7), of Turfitt (8), and of Kirk (9) of particular value.

Description of the means of evaluating the effects of various industrial poisons will be found given in detail in the various publications referred to in the succeeding text. It will be noted that a considerable latitude of experimentation is necessary in order to study the effects of a given industrial poison.

The degree of exposure (that is, the total amount of substance to which an animal has been exposed for a given time) is, of course, only preliminary to the evaluation of the toxicity of the substance. The behavior of the animal must be observed for this is an index of the manner in which the poison acts. Some substances may cause death immediately or within a few minutes—for example, hydrogen cyanide, hydrogen sulfide, or carbon monoxide. Other substances may act as irritants with symptoms of pain, salivation, vomiting, and purging. Ammonia gas, cadmium oxide fume, and chloropicrin, respectively, produce these effects. Other substances affect the central nervous system and produce characteristic symptoms, such as narcosis, convulsions, and paralysis.

The various symptoms, in general, serve at best only as a rough classification of toxic substances. The effects of poisons are often subtle and a variety of symptoms may be displayed. In chronic poisoning, or in the case of a cumulative poison, anatomical changes may be produced in certain organs or tissues which are characteristic for the

poison. Blood changes may occur with an increase or decrease in hemoglobin, in red or white cells, and often with characteristic morphological changes in either or both the erythrocytes and leukocytes. All these and many other effects must be studied with care in the evaluation of the toxicity of a substance. It will be apparent therefore that the term *toxicity* does not refer to a fixed quantity, such as, say, a constant of nature. On the contrary, it is a descriptive term and is often more clearly understood when applied in relation to other analogous substances. When the toxicity of a substance is evaluated in the broad sense described above, however, the industrial toxicologist is able to advise somewhat definitely the limitation of possible exposure of human beings to industrial poisons.

A further element of caution should be exercised with reference to attempts to evaluate the toxicity of a given substance by any mathematical relationship between the quantities of poison administered and the routes of administration, for it is still necessary to consider the species of animals used. Furthermore, in attempting to apply such a relationship to man, a number of other factors must be considered, not the least of which are age and physical condition. However, in order to satisfy those who must know "how toxic" a substance is, a table of usual industrial poisons is appended (Table IV) which gives the LD<sub>50</sub> values for one species of animal (the rat) and one mode of administration (oral), which have been gathered from the literature and to which I have assigned various groupings and designations. It affords a rough means of comparison and avoids the confusion experienced when one is confronted with a variety of species and methods of administration. Even so, it will be recalled that rats are more sensitive to certain toxic substances, for instance alpha-naphthylthiourea, than other animals. However, in the light of acute poisoning the table is presented for what it is worth and disclaims any effort at finality.

It should be clearly indicated that, while such procedures as those briefly indicated above serve to establish useful limits with regard to industrial poisons, the more funda-

mental aspects of toxicology involve far more extensive and difficult physicochemical and physiological investigation. Various physical factors such as surface activity, solubility, dispersibility, polarity, partition coefficient, particle size, and electrophoretic properties may require study. The mechanism whereby many substances produce toxic effects in man is important and requires careful exploration. The fate of these substances in the body—the changes which organic compounds undergo and the metabolites formed—serves to indicate the means by which the body attempts to reduce their toxicity and thus protect itself against their poisonous effects. This is especially true of organic compounds completely foreign to the body. In their passage through the animal organism these substances interact with the normal biochemical systems which they encounter. The enzymic systems which carry out the oxidations, reductions, hydrolyses, and syntheses in the body may be variously affected. The metabolic processes involved reflect an attempt to reduce or abolish the toxic action or damage to the organism. However, it is not true that the product or products formed are invariably less toxic than the parent substance. For example, Channon and his associates (10) found that 2,4,6-trinitrotoluene (*a*-TNT) is partly converted in the animal organism to 2,6-dinitro-4-hydroxylaminotoluene which is excreted as such in the urine. Furthermore, the biological reduction product of picric acid is picramic acid. In both these cases the end-products are more toxic than the original substances. Nevertheless in the case of many other poisons the toxic substance is converted to harmless metabolites and eliminated. Fundamental investigation of the toxicity of a given substance therefore includes study of the course of the toxic agent through the body, its effects on various organs and tissues during its passage, and the changes produced in the substance by the detoxicating mechanism of the body as indicated by the metabolites formed.

Investigation of toxic substances and in particular of the mechanism of detoxication may ultimately prove to be one of the most fruitful fields of biochemistry, inas-

much as it provides specific knowledge of processes that are not obvious nor come to light except as the need for meeting an unusual or critical situation arises. Enzymatic action which can bring about hydroxylation conjugation, acetylation, or methylation of substances foreign to the body is not only interesting *per se*, but may also give a clearer insight into living processes in general (see Appendix, Table II). The minor metabolic changes which occur with certain toxic substances not only follow curious paths, as for instance in the formation of unusual or unexpected metabolites—such as the partial transformation of benzene to *trans-trans*-muconic acid and aniline to *ortho*-aminophenol in addition to its well-known transformation product, *para*-aminophenol—but may have considerable significance. Furthermore the pattern of biological oxidation is frequently different from that of *in vitro* experimentation, for apparently biological oxidation and other processes do not invariably attack those portions of the molecule which are familiar to the chemist as the most reactive centers. Investigation in this field is at best difficult, frequently slow, and occasionally unrewarding, yet a surprisingly large amount of useful information has been accumulated. Interesting as this is, it is beyond the province of this book to discuss the biological significance of the changes which foreign organic substances undergo in the body. The following pages therefore relate to the direct toxic effects of industrial poisons.

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## PART I

# INORGANIC SUBSTANCES

## ALUMINUM

### Characteristics

Aluminum, Al, density 2.70, melting point 658°C., boiling point 1800°C., is a white metal which is very light and strong in comparison with its weight. It is only slightly attacked by exposure to the atmosphere. Aluminum is easily malleable, may be rolled into thin foil, and possesses high tensile strength. It is trivalent in all its compounds and forms only one oxide,  $\text{Al}_2\text{O}_3$ , which is amphoteric. The metal dissolves readily in hydrochloric acid and slowly in sulfuric acid but is rendered passive by nitric acid. It is prepared commercially by electrolysis of aluminum oxide dissolved in melted cryolite, the carbon lining of the pot acting as the cathode and a graphite rod as the anode. The temperature of the bath is kept at about 1000°C., which is above the melting point of aluminum, which collects as a liquid in the bottom of the cell and is drawn off at intervals. Bauxite, a natural hydrated alumina, is the most important source of aluminum.

### Industrial Uses

The output of aluminum in the United States in 1951 was exceeded only by the peak war year in 1943 and totaled about 1,129,000 short tons despite strikes and power shortages that hampered production (1). The widespread uses of aluminum in industry, including aluminum railroad passenger cars, hopper and refrigerator cars, truck and trailer bodies and buses, aircraft, the superstructure of ships, and foil wrappings, are too extensive for enumeration. Aluminum has expanded and diversified its markets until there are now 3,500 uses for the metal compared with 1,500 before the war. Aluminum enters into the composition of a number of alloys, such as "Duralumin" containing 4 per cent copper, 0.8 per cent magnesium, 0.6 per cent manganese; and "Magnalium" with the composition aluminum 90 to 95 per cent, and magnesium 5 to 10 per cent.

Aluminum bronze contains 88 to 96.1 per cent copper, 2.3 to 10.5 per cent aluminum and small amounts of iron and tin. Aluminum salts are used as mordants in the textile industry, the alums are extensively used in a variety of manufactures and aluminum stearate is used as a stabilizer in various oils and greases. In 1951, a total of 868,958 tons of aluminum salts was produced.

### Toxicity

Aluminum salts, especially the acetate, chloride, and sulfate, have some antiseptic properties and in large doses act as gastric irritants causing nausea and vomiting and, in extreme cases, purging. Even in large quantities the ingestion of aluminum salts is followed by no symptoms beyond those of gastrointestinal irritation and inflammation. There is no evidence of chronic poisoning from the continued ingestion of aluminum salts and therefore there is no danger of poisoning nor adverse effects from food cooked in aluminum utensils.

While cases of sensitivity to aluminum dust have been reported (2, 3, 4), this condition is quite rare and there is no convincing evidence of pulmonary or bronchial injury from exposure to aluminum dust in general. In a representative group of 49 workers in the pottery industry, for instance, who were exposed to fine alumina dust, there was no evidence of pneumoconiosis or other lung disease nor any indication that any system or organ was adversely affected (5). An investigation by the Industrial Pulmonary Diseases Commission of the British Medical Research Council in 1936 of aluminum workers revealed no evidence of pulmonary injury due to the inhalation of aluminum dust (6). A more recent investigation by Hunter and his associates (7) of the health of 92 workers, grinders of Duralumin aeroplane propellers, indicated that there was no evidence that this dust produced any disease of the trachea, bronchi, or lungs. The exposure in this case had been heavy and



37 of the group had been employed for more than 5 years. In this connection the experimental work with aluminum dust is confusing, some investigators claiming that aluminum dust is fibrogenic (8, 9, 10, 11) producing "aluminosis", while others (12) find that aluminum dust rarely produces more than a foreign body reaction. The lungs of animals exposed to aluminum dust were found by de Marche (13) to show considerable proliferation of fibroblasts, monocytes, foreign body giant cells and moderate interstitial substance. However Vintinner (14) found that exposure of animals to high concentrations of fine aluminum dust did not increase their susceptibility to Type I pneumococci.

Shaver and Riddell (15) have reported a number of cases of lung disease occurring in the manufacture of alumina abrasives, a process involving exposure to high concentrations of sintered alumina and silica, both in a fine state of division, and to small quantities of many other substances. The disease is essentially an interstitial lung fibrosis, non-nodular in type. A survey indicated that 35 of 344 individuals exposed to these materials in four industrial plants had definite radiological evidence of disease. There were seven fatalities. (cf. Alundum.)

Extensive investigation has been in progress at various research centers during the past few years with reference to the prevention of silicosis by the inhalation of finely divided metallic aluminum. Outstanding in this respect is the work of Denny, Robson, and Irwin (16), who have shown that aluminum dust can bind or inhibit the solution of silica. King and his associates (17) found a retardation, or possibly a prevention, of silicotic lesions in the lungs of animals exposed daily for 200–400 days to an atmosphere of quartz dust with two per cent of powdered aluminum. Jullien (18) attributes the favorable action of aluminum therapy in silicosis as due to an antispasmodic and bronchodilator effect. Schmidt (19) goes so far as to recommend the spraying of factories with dilute aluminum salt solutions in order to produce rapid flocculation of quartz particles and thereby lessening the silicosis risk. The present attitude towards

aluminum therapy for silicosis in this country is perhaps best stated by E. W. Brown (20) in the report authorized by the Council on Industrial Health of the American Medical Association, to the effect that no convincing evidence of objective improvement either of pulmonary function or by roentgen ray has been forthcoming and that further research is required for application of this form of therapy to man.

Reference has been made to industrial injury from machine operations of aluminum alloys, such as Duralumin and Electron metal (21). The injuries resulting from splinter wounds from these alloys are complicated by the formation of hydrogen beneath the skin but the action is mechanical in nature.

### Analysis

Since the aluminum ion is colorless, the direct colorimetric determination of aluminum is usually based on the formation of a strongly colored lake with a suitable organic reagent. These lakes are regarded as internal complexes of aluminum which exist in colloidal solution or as colloidal aluminum hydroxide on which the organic compound is absorbed with a pronounced change in color. A useful reagent for this purpose is aurintricarboxylic acid or its soluble salts. In a weakly acid (acetate-acetic buffer) or neutral medium, ammonium aurintricarboxylate (aluminon) gives a deep red color with minute amounts of aluminum (22). Other organic reagents for the determination of aluminum include alizarin red S, quinalizarin, 8-hydroxyquinoline, and hematoxylin. Sensitive arc lines for the spectrographic identification of aluminum are 3586.6, 2816.2 (the strongest line in its spectrum), 2652.5, and 2568.0.

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### ALUNDUM

A crystalline alumina,  $\text{Al}_2\text{O}_3$ , formed artificially in the electric furnace is variously known in the trade as "alundum" and as "aloxite". The naturally occurring crystal-

line alumina is corundum which when transparent and blue is the gem sapphire, or when red, the ruby but when colored brown or black and impure, is emery. In the United States in 1945 emery amounting to 7,856 short tons was shipped as crude rock to manufacturers of grinding wheels, abrasive sticks, polishing compositions, and similar materials. Considerable amounts are also used as a nonslip, wear-resistant component in concrete floors.

The commercial abrasive alundum is made from bauxite with iron oxide, some silica, and possibly titanium as impurities. The bauxite is first calcined, then mixed with fine coke and iron borings and heated in a combined arc and resistance furnace. The cycle of the furnace is 24 hours; the electrodes are carbon. The resulting fused mass is broken, crushed, washed, purified by chemical treatment, and made into wheels, sharpening stones and grinding powders. Alundum has a specific gravity of 3.93 to 4.01, and a fusion point  $2000^\circ$  to  $2050^\circ\text{C}$ . Alundum refractories can therefore be used at temperatures up to  $1700^\circ\text{C}$ .

Clark (1), on the basis of 14 years observation of workers in an abrasive factory, found that in factories which provide proper methods of dust removal, the continuous inhalation of artificial abrasive dust (aluminum oxide and silicon carbide) does not produce the symptoms or present the X-ray findings of pneumoconiosis. In reviewing 137 cases exposed to large doses of dust, mostly artificial abrasive, over periods ranging from 10 to 42 years, he found that 42 men showed no silicosis, 12 showed slight silicotic change, 72 the picture of first stage silicosis, and 6 the picture of second stage silicosis (2). He concluded that continued inhalation of artificial abrasive dust composed of aluminum oxide and silicon carbide will not produce disabling silicosis. As to the question as to whether the inhalation of artificial abrasive dust produces an increase in the incidence of pulmonary tuberculosis among those exposed, Clark found the incidence to be no higher in the factory than in the city at large. Furthermore, since twice as many cases appeared in dusty as appeared in nondusty departments of the factory, he concludes



that it is inadvisable for persons who have had pulmonary tuberculosis to work in a department in which large amounts of artificial abrasive or any other dust are present. Gardner (3), upon exposing guinea pigs with arrested pulmonary tuberculosis to inhalation of various dusts including carborundum (silicon carbide), reported that 31.8 per cent of the pigs exposed to carborundum dust later exhibited evidence of progressive tuberculosis. However, Gardner, as reported by Clark, stated that he was unable to show the same activation of pulmonary tuberculosis with aluminum oxide dust as he did with silicon carbide dust. Shaver and Riddell (4) have recently reported definite lung changes in workers engaged in the manufacture of alumina abrasives, a condition now designated as "Shaver's disease". The workers in the vicinity of the electric arc furnaces are exposed to the dense white fumes evolved from the pots. These "fumes" contain large amounts of alumina and silica together with small quantities of other substances, all in a very fine state of division. Three hundred and forty-four individuals in four different industrial plants were exposed to these materials and a survey showed that 35 of these had definite radiological evidence of disease and that there were 13 others with lung changes classified as doubtful. Seven fatalities have occurred and in several cases the disease has progressed rapidly and has produced serious disability. It is essentially an interstitial lung fibrosis, non-nodular in type with profound emphysema accompanying the invading fibrosis. Emphysematous blebs and bullae occur on the visceral pleura and are apt to rupture spontaneously and give rise to pneumothoraces, according to Shaver and Riddell (*cf.* also 5, 6, 7). However, the etiology of Shaver's disease has not been definitely established. Both Jager (8) and Gartner (9) believe colloidal or fine amorphous silica, not alumina, to be the cause of the disease.

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## AMMONIA

### Characteristics

Ammonia,  $\text{NH}_3$ , is a colorless gas with a pungent odor, a vapor density of 0.597, a melting point of  $-77.7^\circ\text{C}$ ., and a boiling point of  $-33.3^\circ\text{C}$ . It is easily liquefied and is extremely soluble in water with which it forms ammonium hydroxide. Strong ammonia water contains 28 to 29 per cent of ammonia and at  $25^\circ\text{C}$ . has a specific gravity 0.90 that of water. Ammonia is a product of the putrefaction of nitrogenous substances. In the vicinity of putrefying substances, the amount of ammonia may be of the order of 15 to 1500 parts per million of air (1). Except, however, in the immediate neighborhood of the decomposing material ammonia does not exist in the air in the free state but is combined usually as the carbonate. Ammonia is one of the by-products formed in the destructive distillation of coal for the production of coal gas, coke, and tar. It is made synthetically when nitrogen and hydrogen are mixed and brought in contact with a catalyst, such as specially prepared iron granules at elevated temperature and under high pressure. The Haber process in Germany, the Claude in France, the Casale in Italy, and the American in the United States utilize this principle. Ammonia is usually transported either in liquefied form in steel cylinders or in tank cars, or in

drums or carboys dissolved in water as the hydrate.

### Industrial Uses

Ammonia is a hazard in numerous industries. It is used as a refrigerant in cold-storage plants and for the manufacture of artificial ice, in petroleum refining, in the treatment of steel, water purification, in the fertilizer industry, in the manufacture of sulfuric and nitric acids, drugs and chemicals, and in bottling plants for household ammonia.

### Toxicity

Ammonia in the air in low concentrations is readily detected by its distinctive odor; in high concentrations it acts violently upon the respiratory tract and causes a choking sensation. In addition to its action on the respiratory reflexes which causes coughing and the arresting of respiration, it also has an immediate effect on the conjunctiva and the cornea. Chronic bronchial catarrh, secretion of saliva, and the retention of urine have also been noted. According to Boyd and his associates (2), there is an increased output of respiratory tract fluid but little change in the water content of the lungs. Yet in acute pulmonary edema, such as occurs in ammonia gas poisoning, the lungs are generally held to be water-logged. Although there is no change in serum chloride, an increase above normal in blood hemoglobin beginning about 24 hours after gassing has been noted. Mass poisoning from ammonia gas occurred in a London shelter early in the late war in which 47 cases of ammonia gas poisoning were hospitalized and in which 13 people died (3). Most of these deaths resulted from pulmonary edema. A similar accident occurred in which three individuals died and three were overcome from effects of ammonia gas when the connection of a tank car of ammonia was broken while unloading (4). The three who survived had eye injuries and pains in the abdomen, as well as intense nervousness. However, ammonia is not considered to have a direct action on the nervous system. In animal experiments designed to investigate possible chronic toxicity resulting from exposure to the fumes of ammonia, Weatherby

(5) could find no significant evidence of such an effect, although long exposure resulted in mild changes in various organs and tissues especially noticeable in the spleen. The least amount detectable by smell is 53 parts per million (6).

### Analysis

Several sensitive methods have been proposed for the detection of ammonia or the ammonium group, such as the well-known Nessler's reagent and the test with *p*-nitrobenzene diazonium chloride which gives a red color with ammonium salts. Ehrenberg (7) has proposed a novel radiometric method for the detection of extremely minute amounts. For the determination of ammonia as an aerial contaminant, samples may be taken by drawing known amounts of the air through slightly acidified water in a sintered glass bubbler followed by adequate dilution and direct Nesslerization. Any of the many proposed micro-determinations for the evaluation of ammonia may be applied. For very small quantities of ammonia, Mason and Rozzell (8) have adapted a Nesslerization procedure suitable for determination of quantities of ammonia varying over the range of 1 to 10 micrograms with an accuracy of  $\pm 5$  per cent.

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### ANTIMONY

#### Characteristics

Antimony, Sb, atomic weight 121.77, is a lustrous white metal which, following slow



cooling, exhibits a coarsely laminated crystalline fracture but which possesses a granular structure when rapidly chilled. It is a relatively soft metal having a hardness of 3.0 to 3.5 on Moh's scale. The most representative melting point is  $630^{\circ}\text{C}$ ., its density  $20^{\circ}/4^{\circ}$  when mold-cast is 6.690, and its boiling point is  $1440^{\circ}\text{C}$ . Antimony is so brittle that it can be powdered. It does not undergo change on exposure to the air at ordinary temperature and is only very slightly and slowly soluble in cold water. Clarke found its solubility to be 0.19 milligram in 25 minutes (1). The metal burns with a bluish-white flame without volatilizing, but at about  $900^{\circ}\text{C}$ . in the presence of oxygen gives off fumes which have a smell resembling garlic. The vapor pressure of antimony at various temperatures (2) is much less than that of arsenic at the corresponding temperature. At  $500^{\circ}\text{C}$ . the vapor pressure of arsenic is 100 millimeters of mercury, while that of antimony is  $10^{-3}$  millimeters of mercury at that temperature. This difference in volatility is important from the point of view of industrial exposure and is also of incidental interest in connection with the analytical determination of antimony in organic material.

In connection with industrial exposure to the various antimony dusts, it is of interest that finely divided antimony dust can remain suspended in air longer than would be anticipated with a heavy metal. After 1 hour a dust of 8.8 milligrams of antimony per cubic foot of air was found to settle only to the extent of 2.5 milligrams per cubic foot (3). Furthermore, antimony trioxide fume remains in suspension in air for a considerable length of time whereas the sulfides tend to settle out fairly rapidly and antimony metal dust occupies an intermediate position.

When certain alloys containing antimony are treated with acid and subjected to electrolytic action, when certain antimony compounds are treated with steam, or whenever nascent hydrogen comes in contact with metallic antimony or with a soluble antimony compound, a colorless gas, stibine ( $\text{SbH}_3$ ) is evolved. In many of its properties, stibine is similar to arsine. However, it lacks the stability of arsine and, perhaps because of this fact, stibine poisoning has never at-

tained the importance of arsine in industrial hygiene. Stibine is decomposed at a lower temperature than arsine and is also decomposed by such substances as rubber or even the walls of the containing vessel, especially if slightly etched. Rapid decomposition occurs at temperatures above  $150^{\circ}\text{C}$ . Stibine is oxidized by air or oxygen, even at low temperatures, and as might be expected, is readily decomposed by a number of substances, such as the halogens, sulfur, and most oxidizing reagents. It solidifies when cooled in liquid air and melts at  $-8.8^{\circ}\text{C}$ ., forming a colorless liquid which boils at  $-17^{\circ}\text{C}$ . The gas is heavy and has a vapor density at  $15^{\circ}\text{C}$ . and 754 millimeters of mercury of 4.36 (specific gravity of air = 1). The gas has an extremely unpleasant smell which is difficult to describe.

### Industrial Uses

In 1951, antimony metal, oxide, and sulfide, having a total antimony content of 34,111 tons, were produced in the United States, and in that year 43,818 tons were consumed in the manufacture of various items (4). In addition, secondary antimony recovered from lead-base (such as old battery plates) and tin-base alloys totaled 17,148 tons. The metal products in which antimony is used are listed in order of amount: antimonial lead (5,920 tons), bearing metal, battery metal, type metal, cable covering, sheet and pipe castings, collapsible tubes and foil, ammunition, and solder. The nonmetal products listed in the same order are as follows: flame-proofed textiles (7,675 tons), paints and lacquers, frits and ceramic enamels, glass and pottery, sodium antimonate, antimony trichloride, ammunition primers, and matches.

### Toxicity

Cases of antimony poisoning in industry are rare, although certain antimony compounds are extremely poisonous and warnings concerning the potential danger of antimony in industry have been published from time to time. Both Oliver (5) and Hamilton (6) have referred to the excessively dusty condition of plants manufacturing or using antimony trioxide and the trisulfides and pentasulfides, and have

pointed out a corresponding absence of disease attributable to antimony beyond occasional dermatitis. In smelting operations fumes of antimony and of antimony oxide are abundantly given off. The breaking up of the solid metal is also a dusty operation. It has been shown (3) that finely divided metallic antimony occurring as dust is more toxic than certain other industrial antimony compounds. In the manufacture of antimony trioxide, workers in the bag houses or condensing chambers engaged in knocking down the oxide in the bags or in cleaning the chambers, as well as those occupied in packing the oxide, are exposed to a great deal of oxide dust. Feil (7) found that a few workers, who were engaged in smelting antimony, exhibited symptoms of dermatitis and conjunctivitis. The experimental work of Bradley and Fredrick (8) indicates in general that antimony compounds are more toxic than similar lead compounds. Recent inhalation experiments in which animals were exposed to antimony trioxide indicate that some pathology is involved (9). Smith (10), studying the excretion rate of tartar emetic in man by means of radio-antimony, found the 50 per cent excretion time to be of the order of 500 hours. Renes (11) reported 69 cases of illness from exposure to fumes among workers during 5 months of operation of an antimony smelter. Gross and his associates (12) found that calcium halophosphate phosphors containing 1 per cent of antimony caused no evidence of either acute or chronic toxicity when tested on rats and rabbits, although an endogenous lipid pneumonia occurred in these animals (13) following inhalation or intratracheal insufflation of large amounts of antimony trioxide. However, Brieger and his associates (14) found that exposing animals to 3.07 to 5.6 milligrams per cubic meter of antimony trisulfide dust for 6 weeks resulted in definite and consistent disorders of the heart and parenchymatous degeneration of the myocardium in these animals. These investigators suggest periodic electrocardiographic examination of antimony workers.

The physiological action of stibine greatly resembles that of arsine, death occurring very quickly on exposure to such a

high concentration as 1 per cent gas in air. In a concentration of 0.01 per cent gas, death occurs in a few hours. Stibine attacks the central nervous system and the blood. In acute poisoning, the symptoms are headache, nausea, weakness, slow breathing, and weak and irregular pulse. The gas has a hemolytic effect on blood and causes pronounced morphological changes in the red cells, producing, in particular, characteristic "spine cells" in animals subjected to various concentrations of the gas (15). Chronic stibine poisoning has not been observed in man. Pure stibine prepared under laboratory conditions is unquestionably very toxic. However, the literature has failed to disclose a clear-cut fatal case of stibine poisoning in man. When stibine poisoning has been reported, it has usually been questionable whether the poisoning was really due to stibine or whether it was due to arsine, hydrogen sulfide, or phosphine.

Cases of possible stibine poisoning arising from exposure to gases produced by the quenching of hot metallic dross with water have been reported (16, 17). The addition of water to a hot antimony metal dross containing aluminum causes the formation of nascent hydrogen which reacts with the antimony, arsenic, and sulfur present to form  $\text{SbH}_3$ ,  $\text{AsH}_3$ , and  $\text{H}_2\text{S}$ , respectively. In the cases just referred to, three employees exposed to these gases in a building became ill within a few hours and complained of marked weakness, headache, nausea, severe abdominal and lumbar pain, and hematuria. The hemolytic effect on the blood was the most outstanding laboratory finding. Recovery followed hospitalization and treatment with intravenous glucose, blood transfusions, and the administration of ferrous sulfate.

### Analysis

While most of the usual methods for the determination of antimony are suitable for material containing fairly large amounts, such as rafter dust, ores or minerals, more delicate procedures are necessary for the determination of traces of the metal or its compounds as aerial contaminants. Relatively few colorimetric methods have been



found for the determination of antimony. However, tetraethylrhodamine (Rhodamine B), which undergoes a change in color from red to violet in the presence of antimony, has been found to be a useful reagent. With this reagent pentavalent antimony in acid solution forms a red, water-insoluble, stable compound which is soluble in organic solvents (18). The reagent 9-methyl-2,3,7-trihydroxy-6-fluorone has also been recommended for the detection and colorimetric analysis of antimony (19). The sensitivity to this substance is 1:5,000,000 and only a limited number of substances interfere. The detection and estimation of between 10 and 30 micrograms of stibine may be rapidly carried out by the method of Webster and Fairhall (20). Distinctive arc lines for the spectrographic detection of antimony are 2877.9, 2790.4, 2528.5, and 2311.5. Although antimony shows up with moderately small amounts in the arc, spark methods yield the highest sensitivity for this element.

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## ARSENIC

### Characteristics

Arsenic, As, atomic weight 74.91, has a melting point of 814° at 36 atmospheres pressure and a sublimation point of 611° C. The density of arsenic is 5.7 and it exists in a number of allotropic forms. Yellow arsenic, which volatilizes readily, is extremely poisonous and phosphoresces in air at room temperature. The semi-metallic form of arsenic is steel gray in color with a bright luster. It is very brittle and is a good conductor of heat but a rather poor conductor of electricity. Arsenic forms three oxides, namely, arsenious oxide or arsenic trioxide ( $\text{As}_2\text{O}_3$ ), arsenic pentoxide ( $\text{As}_2\text{O}_5$ ), and arsenic tetroxide ( $\text{As}_2\text{O}_4$ ). The latter is only of academic interest. The pentoxide is the anhydride of arsenic acid and is the primary material for all arsenical insecticides. However, the trioxide or white arsenic is the most abundant commercial arsenical compound and from it practically all manufactured arsenical compounds are originally derived. In common with several other members of its group, arsenic forms a compound with hydrogen, arsine,  $\text{AsH}_3$ , which is a colorless highly poisonous gas with a strong garlic odor. Arsine is formed whenever

nascent hydrogen is produced in the presence of arsenic or arsenic-bearing substances.

### Industrial Uses

White arsenic consumption dropped from an all high of 51,083 short tons in 1943 to 28,869 short tons in 1951. One-half of the amount produced in 1945 entered into the preparation of agricultural insecticides for the purpose of combating the cotton boll weevil, the codling moth, and the gypsy moth, which cause such widespread agricultural loss of cotton, apples, and pears. The use of arsenic in weed killers and in the glass industry accounts for a substantial share of the balance. According to the United States Bureau of Mines, the domestic output of white arsenic has at no time been adequate to meet domestic requirements and the United States will probably continue to be a substantial importer. Smaller amounts of arsenic are used in medicinal arsenicals, alloys, wood preservatives, cattle dip, dye-stuffs, and paint.

### Toxicity

From an industrial health point of view, arsine is the principal factor of importance with reference to arsenical poisoning. While an extensive literature exists with reference to poisoning from arsenic trioxide or other arsenical preparations, it has largely been built up on the basis of the use of arsenic with criminal intent and hence the administration of arsenical preparations by mouth (Truhaut, 1). On the other hand, exposure in industry to arsenical compounds relates largely to the inhalation of dust or fume. In the refining and smelting of arsenical ores or in smelting metals containing arsenic and in the subliming of white arsenic, workers may be exposed to the fumes of the metal or its oxides. Workers are also exposed to dust in the manufacture of Paris green (cupric acetoarsenite), Scheele's green (cupric arsenite), and of lead and calcium arsenates for insecticidal purposes. Arsenical dusts produce troublesome skin lesions resulting at an early stage in an edematous condition with inflammation and finally ulceration. Wherever the dust comes in contact with the skin and is held by perspiration

in folds (as around the edges of respirators), ulcers develop. Perforation of the nasal septum is common. Slow absorption also occurs and is evidenced by bronzing. In severe cases gastric symptoms occur. Although arsenic has long been associated with cancer as a causative agent an interesting recent study by Snegireff and Lombard (2) with reference to cancer in industry led these investigators to conclude that the handling of arsenic trioxide in industry does not produce a significant change in the cancer mortality of employees. Lead arsenate which is commonly used as an insecticide has been shown to be broken down in the body in man with the subsequent excretion of most of the arsenic from the kidneys (3). The pronounced solubility of dilead *o*-arsenate in gastric juice is sufficient to account for the breakdown of lead arsenate in passing through the gastrointestinal tract (4). The arsenate radical apparently either decreases the absorption or increases the excretion of lead (5). Soluble arsenates have also been found to decrease the storage of lead (6). The "normal" arsenic content of tissues and excretions has frequently been investigated and a normal urinary arsenic value of 0.017 milligram of  $\text{As}_2\text{O}_3$  per 100 cubic centimeters of urine is indicated by the investigations of Watrous and McCaughey (7).

The action of arsine is different from that of arsenic salts or compounds in general. In industry arsine usually results from pickling operations in which arsenic exists as an impurity either in the metals or the acids used. It has been shown, however, that even quenching material containing arsenides with water has caused arsenical poisoning and deaths (8). Additional cases of this type have been reported recently (9, 10). Chronic arsine poisoning has also been reported by Bulmer and his associates (11) with workers employed in the extraction of gold where the ore contained a small percentage of arsenic, for in cleaning the filter leaves with hydrochloric acid, arsine was evolved. A somewhat similar case of arsine poisoning recently occurred during the cleaning of an iron water jacket and was caused by pouring dilute commercial hydrochloric acid through the pipes of the jacket (12). The specific effect



of arsine is related to its affinity for the hemoglobin of the red blood corpuscles and the symptoms of acute arsine poisoning result from hemolysis of the red blood cells with resulting anemia and jaundice. It has been suggested that arsine is carried unchanged to the various tissues by loosely combining with the erythrocytes (13). Fatal termination is frequent.

### Analysis

The great importance of arsenic from a toxicological point of view and the extreme sensitivity of the various methods has resulted in the accumulation of immense amounts of literature devoted to the analytical detection and estimation of this substance. The conventional Marsh and Gutzeit methods which depend on the formation of arsine and its detection are convenient and satisfactory within certain limits. The gold chloride test paper method of Turfitt (14) is a particularly useful test for arsenic. Of the various colorimetric procedures for the micro-determination of arsenic, that of Sandell is both accurate and sensitive (15). In this method, the material, freed from substances that prevent complete evolution of arsine, is so treated that the arsenic is quantitatively evolved as arsine. This, in turn, is absorbed in an acid solution of mercuric chloride containing permanganate and the arsenic thus oxidized to arsenate can be determined by the addition of an excess of ammonium molybdate-hydrazine sulfate reagent which yields molybdenum blue in proportion to the amount of arsenic present. This method is particularly applicable to amounts of arsenic within the range of 1 to 15 micrograms with an accuracy of 5 per cent. Arsenic may also be detected qualitatively by *n*-ethyl-8-hydroxy-tetrahydroquinoline hydrochloride, which gives a reddish-brown color in spot tests in the presence of ferric chloride (16). The arc spectrum for arsenic is very poor and there are a number of interfering lines. However, the following lines—2860.5, 2780.2, and 2349.8—are useful for spectrographic identification.

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## ASBESTOS

### Characteristics

Asbestos, amianthus, earth flax, stone flax, mountain cork, is a characteristically silky, fibrous mineral, the composition of which varies with its source. The form known as chrysotile is derived from serpentine and is a hydrous magnesium silicate containing from 12.5 to 14 per cent water of crystallization.

About 95 per cent of commercial asbestos is chrysotile. Chrysotile has the silkiest and strongest fiber and can be spun. The fibers may be as long as 6 inches in length. Asbestos derived from amphibole occurs as a variety of minerals consisting of iron, calcium, and magnesium with little water of constitution. The latter type of asbestos consists of short fibers and is usually inferior to that derived from serpentine. Amphibole asbestos (anthophyllite) while not so suitable for spinning is more stable chemically than chrysotile and more resistant to acids and heat.

Canada has been an important source for the chrysotile asbestos used largely in the United States. The Canadian asbestos industry is centered in the Thetford Mines area of the Province of Quebec. A new source for chrysotile type asbestos is a large quarry on the eastern shoulder of Belvidere Mountain in Vermont which was opened in the summer of 1944. This deposit is of importance because it represents the only large source of long-fibered chrysotile so far found in the United States. Deposits of amphibole asbestos are mined in Georgia and North Carolina.

### Industrial Uses

Asbestos is an important substance in industry and consumption in the United States for 1951 amounted to 796,992 short tons (1). Due to its fibrous nature, flexibility and heat-resistant properties, it is used extensively for valve packings, gaskets, boiler lagging, and pipe covering in industrial plants and as friction material in the automotive industry. A considerable market exists in the building industry for asbestos-cement products, heat insulation, and fireproofing. The utilization of asbestos for fibers for spinning in the manufacture of asbestos clothing for fire fighting is an important use for asbestos. The largest single outlet for asbestos in manufactured products in 1944 was for clutch facings, and next in quantity of output were brake linings. Asbestos roofing consumed the third largest amount of asbestos in that year.

### Industrial Injury

The inhalation of asbestos dust produces a condition known as asbestosis. While cer-

tain other minerals of minor importance have been shown to produce lung fibrosis, asbestos is the only important silicate apart from talc and mica which does not contain free silica and yet produces pulmonary lung fibrotic changes leading to disability and death. Asbestosis occurs chiefly in industrial plants where asbestos is fabricated. The spinning and weaving of asbestos in combination with other textiles results in exposure of workmen to asbestos dust. The long-continued inhalation of asbestos dust results in a form of pneumoconiosis. The primary effect of inhalation of asbestos dust is an interstitial pulmonary fibrosis. On an X-ray film the shadows cast by this type of fibrosis resemble ground glass in appearance and usually extend over the lower portions of the lung fields, frequently being heavier on the right side (2). Unlike silicosis, nodular fibrosis has not been detected in asbestos workers (3). The fibrogenic action differs from that of silica in that the effects are produced only by long asbestos fibers while the very short asbestos fibers appear to have little or no effect. The long fibers apparently block the finer bronchioles and produce fibrotic changes as a result of irritation. A progressive dyspnea, variable cough, substernal chest pains, decreased chest expansion, weakness, emaciation, clubbed finger tips, and curved fingernails are the chief symptoms of asbestosis, as in silicosis. A characteristic finding in asbestosis is that of asbestos bodies in the lungs and in the sputum (4). The so-called asbestos bodies are apparently formed only in the lungs and may be demonstrated microscopically on sectioning lung tissue or in the sputum. The core of the body is an asbestos fiber which is surrounded by protein deposits. Unstained specimens are golden yellow or golden brown. They are not stained with ordinary histological stains but may be demonstrated by the Prussian blue staining procedure. The reaction to the fibrous needle in the tissue which becomes manifest in exudate cell infiltration is accompanied by numerous giant cells containing foreign particles and an increase of diffuse interstitial connective tissue and fibrosis. While the essential reaction to asbestos particles is considered to be chemical by many investigators others consider the



pathogenesis of the disease to be mechanical (5) in nature. For instance, the investigations of Vorwald and his associates (6) indicate that the mode of action of the long asbestos fiber is mechanical rather than chemical in nature. When the lungs are examined by the naked eye after death, they are large and densely fibrotic. Often the lung is completely adherent to the chest wall and, in advanced cases, to the diaphragm with the formation of a thick and extremely dense layer of fibrous tissue. Four main complications and sequelae of pulmonary asbestosis are purulent bronchitis, bronchial pneumonia, pulmonary tuberculosis, and emphysema (7). Several cases of asbestosis have been reported which progressed to a fatal termination with heart failure and without evidence of infection or other complicating disease (8). Any appreciable decrease in the amount of asbestos dust will cause a decrease in the incidence and severity of asbestosis (9). In a recent study of 40 cases of asbestosis at necropsy, Lynch and Cannon (10) found support for the belief that fibrosis does not progress indefinitely after cessation of exposure. It would appear that if the dust concentration in asbestos factories can be kept below 5 million particles per cubic foot, new cases of asbestosis would not arise (2). Cartier (11) has found cases of asbestosis only in those employed for at least 14 years and exposed to air containing at least 5 million fibrous particles varying in length from 10 to 250 microns per cubic foot of air. Doll (12) has concluded from a study of 105 necropsies of individuals employed at an asbestos works that lung cancer is a specific hazard of asbestos workers.

### Analysis

While the analysis of asbestos dust as an aerial contaminant is not of particular importance, its microscopy and above all the evaluation of the number of particles per cubic foot of air is of paramount importance. Air samples may be secured by the impinger method using 25 to 50 per cent alcohol as a collecting medium and dust counts made by the usual method. Microscopic examination of the dust reveals typical asbestos fibrous particles which may be accompanied also by cotton or other textile fibrous materials in

samples taken from the air of weaving factories. The index of refraction being only slightly greater than that of Canada balsam, the relief is low. Other forms of asbestos than chrysotile have somewhat higher indices of refraction. Extinction is parallel except in the case of tremolite which has oblique extinction. The birefringence of chrysotile is moderate  $n_v - n_a = 0.013$ . The maximum interference color is bright yellow of the first order. The air sampling of asbestos dust both by the impinger method and by the electrostatic precipitator method is discussed in detail by Fehnel (13).

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## BARIUM

### Characteristics

Barium, Ba, atomic weight 137.36, density 3.5, melting point 850° C., and boiling point 1140° C., is a yellowish-white, slightly lustrous, soft metal which is somewhat malle-



able and is very easily oxidized. Metallic barium is of little commercial importance and barium occurs in commerce chiefly as barite,  $\text{BaSO}_4$ . Barium is divalent and forms only one series of compounds.

### Industrial Uses

During 1951 the consumption of barite in the United States amounted to 950,900 short tons and had nearly doubled in amount over that reported 10 years previously. Over 62 per cent of the tonnage was used in oil-well drilling muds. The amount used for lithopone manufacture in 1951 was 107,094 short tons, while the production of barium chemicals accounted for 132,268 short tons; 25,779 tons were used in glass making, 28,000 tons for paint filler and 15,000 tons were used in the rubber industry (1). Barite is the only domestic barium mineral in commercial use although a small amount of witherite,  $\text{BaCO}_3$ , is imported from Great Britain, which is the world's source of this material. Metallic barium is used for the removal of residual gases in electronic tubes in which case it is usually alloyed with either magnesium or aluminum. Both barium oxide and barium nitrate are used for pyrotechnic purposes and found some application in tracer bullets during World War II and in the new thermite incendiary bombs which were used in Japan. Barium hydroxide is used to a certain extent in beet sugar purification. Barium sulfate is extensively used for roentgenological examination of the gastrointestinal tract. Barium stearate is used as a stabilizer and as a mold lubricant in the rubber and plastics industries where the mold temperatures are high.

### Toxicity

Cases of barium poisoning have for the greater part arisen from the ingestion of barium carbonate in rat poisons or from mistakes which have occurred in dispensing the carbonate or sulfide instead of the sulfate for roentgenological purposes. A similar mistake occurred in which barium chloride was dispensed in place of sodium chloride (2). A case of mass poisoning of 85 soldiers has been reported in which barium carbonate had been erroneously added to

flour (3). Numerous cases of poisoning have been reported in the Kiating and Wutungehiao provinces of China due to contamination of table salt with barium chloride (4, 5, 6). While the fatal dose of barium is probably 0.8 to 0.9 gram of the chloride (7), recovery has occurred from much larger doses where prompt treatment was administered. The ingestion of soluble barium salts causes vomiting, colic, and violent diarrhea. Hemorrhages have been found in the stomach, intestines, and other organs. Sodium chloride solutions containing barium chloride fed or injected in rabbits and dogs caused nausea, vomiting, diarrhea, salivation, and weakness in extremities followed by paralysis (8, 9, 10, 11). Guareschi and Boari (10) found that the hypodermic administration of barium chloride in amounts of 23 to 25 milligrams caused death of guinea pigs, amounts of 15 to 19 milligrams caused toxic effects, but no lesions were produced by 2-milligram quantities. Although barium poisoning has not been of much significance industrially, barite pneumoconiosis has been reported among workers in barite mills (12). Pendergrass and Greening (13) have reported a case of baritosis where a worker was exposed to finely divided particles of barium sulfate, and bronchial irritation due to barium carbonate dust has been noted in a factory where bomb casings are heated in barium carbonate (14). The depilatory action of barium sulfide has been a source of complaint among workers preparing lithopone and whitening of the hair has also been reported among barium workers.

### Analysis

The analytical determination of small amounts of barium is somewhat difficult, although the properties of both the sulfate and chromate are such that this separation would appear relatively simple. A chromate method has been devised, however, which, in spite of the appreciable solubility of barium chromate especially in the presence of other salts, may be usefully applied (15). While the colored barium salts of tetrahydroxyquinone and rhodizonic acid are too soluble to be of much value in trace analysis, a method for the determination of barium

dust as an aerial contaminant has been devised which utilizes the selective formation of mixed crystals of barium sulfate-potassium permanganate when barium sulfate is precipitated from solutions containing potassium permanganate (16). The principal spectral arc lines of barium are 5535.54, 4934.09, and 4554.04.

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## BERYLLIUM

### Characteristics

Beryllium, Be, atomic weight 9.02, density 1.73, hardness 7.5–8.0, melting point 1300° C., boiling point about 1500° C., is a dark gray metal resembling steel in appear-

ance and luster, and is hard enough to scratch glass. It is a very light metal having about the same density as magnesium. The salts are sweet in taste. Beryllium yields only one series of salts derived from the one oxide, BeO. The normal salts have an acid reaction in aqueous solution, hydrolysis of the fluoride and sulfate being particularly marked, so complete in fact the metallic zinc dissolves in an aqueous solution of beryllium sulfate with the evolution of hydrogen. Beryllium is differentiated from other members of the alkaline earth group by the insolubility of its oxide. It may be distinguished from aluminum by the solubility of beryllium hydroxide in an excess of sodium bicarbonate—probably due to the formation of a complex bicarbonate ion, a property which is of use in its analytical separation.

### Industrial Uses

World production of beryllium ore in 1945 (854 metric tons) was 83 per cent less than in 1943 when special war uses induced the much larger output (1). World production of beryllium concentrates in 1951 was 5,720 metric tons. Beryllium enters into industry in several forms, as beryllium-copper alloys, as the oxide, as metal, and as beryllium salts, and to a very minor extent as beryllium-nickel or beryllium-aluminum. An increasing use because of the employment of industrial radiography has been for windows of X-ray tubes where it permits the passage of "soft" or long wavelength radiation. Beryllium oxide or zinc beryllium silicate was formerly used as a phosphor giving a yellow-white light in fluorescent lamps. Another growing use of the oxide is for refractory crucibles and shapes. Beryllium-copper alloy is distinguished by its hardness, high tensile strength, and resistance to corrosion and fatigue, while its electrical conductivity is but little different from that of copper. The alloy is finding an increasing range of application because of its unusual properties.

### Toxicity

An investigation of the physiological action of beryllium and its compounds reported in the National Institutes of Health



Bulletin, *The Toxicology of Beryllium* (2), indicates that there is no specific toxic action attributable to the beryllium ion. In this study, animal experiments were made in which a number of beryllium compounds were injected intraperitoneally into guinea pigs at various concentrations, beryllium compounds were administered orally to both young rats and guinea pigs, and finally guinea pigs were exposed to the dust of beryllium compounds in high concentrations and over long intervals of time with no indication that beryllium is inherently toxic. There was no evidence of beryllium rickets. Exposure of both guinea pigs and rats to the fumes arising from the electrolysis of molten fluorides containing beryllium fluoride or oxyfluoride shows that these fumes are decidedly toxic. The distribution of beryllium in the various organs and tissues of the experimental animals indicates but very little storage of beryllium following exposure to large amounts whether by mouth, by inhalation, or by intraperitoneal injection.

The inhalation of beryllium sulfate dust was shown to be injurious to guinea pigs (67 per cent mortality in one exposure), but when the more neutral potassium beryllium sulfate was substituted the animals were able to tolerate much larger doses (no mortality in heavy exposures daily for 7 days). Later experimental work, using rabbits as experimental animals, has confirmed this earlier finding. Beryllium sulfate hydrolyses freely and probably causes strong local irritation at those sites to which the material is carried on inhalation, whereas inhalation of a soluble neutral salt such as potassium beryllium sulfate, while yielding as high or higher concentrations of beryllium, does not produce this injury. If beryllium were a protoplasmic poison, both beryllium sulfate and potassium beryllium sulfate should show similar effects.

There have been many reports in recent literature concerning the industrial hazards associated with the production of beryllium. Shilen, Galloway, and Mellor, in 1944 (3), reported the health hazards incident to the extraction of beryllium. Kress and Crispell (4) have reported cases of chemical pneumonitis in men working with fluorescent powder containing beryllium. Van Ordstrand

and his associates (5, 6) have reported respiratory tract disease and dermatological effects which they have observed in the beryllium industry during 1941 to 1945. The fatal cases described in this report resulted from chemical pneumonitis presumably due to exposure to mist or dust of beryllium sulfate. A similar chemical pneumonitis developed in an additional 33 workers at various occupations in these plants. While the hazard due to dust and fume that exist in the plants was undeniable, and the hazards of such exposures were indicated in the bulletin referred to (2), further direct experimental evidence with reference to a possible physiological response to beryllium is needed. When beryllium sulfate or fluoride comes into contact with cuts or abraded surfaces of the hands, rather deep ulcers are formed which are slow in healing. The beryllium salts of weak acids have been shown to have far less effect on the skin (7). In connection with the manufacture of fluorescent lamps, a number of cases, which were designated as sarcoidosis, were reported in 1943 in the Massachusetts area. Since beryllium oxide is one of the constituents of the fluorescent powder, this substance was suspected as the etiological factor in the production of sarcoidosis. Hardy and Tabershaw (8) reported 17 cases of delayed chemical pneumonitis occurring in workers exposed to phosphors containing beryllium in a plant manufacturing fluorescent lamps. There have been six deaths. The feature that separates the present group from previous reports in the literature is the delay in onset following common exposure and progression of the disease in spite of change in environment. These cases were attributed, if not directly, at least by implication, to beryllium poisoning. Grier, Nash, and Freiman (9) have recently described three cases of subcutaneous granuloma arising from cuts with broken fluorescent lamp tubes. The authors ascribe the granulomatosis to beryllium. Eighty-five cases of beryllium intoxication in a factory extracting beryllium by the fluoride process have been reported by Ginabat (10). These cases were cured without sequelae, but resulted in the loss of 778 work days. Ginabat stressed the hazards of beryllium production and stated that ener-



getic prophylactic measures should be taken to suppress the risks involved. Shilen and his associates have also recently reported an extensive investigation of the health hazards of beryllium extraction and alloy manufacture in which they made careful measurement of the fluoride and beryllium content of the air at various stations in the plant, as well as dust concentration and count and nitric oxide fumes from the pickling vats (11).

The exact etiology of many reported cases has not been established as other than beryllium, and, since inhalation of the dust, mist, and fume of certain beryllium salts, such as the fluoride, sulfate, chloride, and oxyfluoride, is known to be hazardous (2), it is important to maintain environmental conditions as free as possible from the smoke, mist, or fumes of these salts.

A great number of "cases" implicating beryllium have been reported where only infinitesimally minute amounts of beryllium could possibly have been concerned. On the other hand Shilen and his associates (12) have recently completed a 10-year study of a beryllium plant which produces approximately 90 per cent of the extracted and alloyed beryllium made in the United States. During this 10-year period beryllium exposures have run as high as 8.8 milligrams per cubic meter of air, many workers have been employed for 12 years or more, and urinary analyses for beryllium of these employees have indicated definite absorption. Shilen found that "there is nothing indicated in the entire study to lead to the conclusion that this plant presents more hazardous working conditions than any other plant in the metal industry."

The authenticated facts that workers are daily exposed to the dust and fumes of a variety of beryllium compounds, and yet can remain well and healthy, contrasts with the many theories put forth to indicate that beryllium is an extremely toxic substance. There is pressing need for further careful scientific investigation in this field.

### Analysis

The analytical separation and identification of beryllium even when present in quantity is difficult. The beryllium ion is not

colored in any of its compounds and the close similarity of beryllium and aluminum in their chemical behavior complicates the determination of beryllium. Sodium bicarbonate is useful, however, in separating beryllium from aluminum, as aluminum hydroxide is precipitated by this reagent while beryllium remains in solution. 1-4-Dihydroxyanthraquinone-2-sulfonic acid (2) and 1-amino-4-hydroxyanthraquinone (13) give useful color and fluorescence tests, respectively. Sensitive arc lines for the spectrographic detection of beryllium are 3321.35, 3321.08, 3131.06, and 2348.62.

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## BISMUTH

### Characteristics

Bismuth, Bi, atomic weight 209, is a hard brittle, lustrous, pinkish silver-white metal which is usually covered with a film of bismuth oxide. It has a density of 9.78 (20° C.), melts at 271° C., and boils at 1435.5° C. When the molten metal is cooled it crystallizes in cube-like rhombohedrons and while doing so it expands considerably. Because of its internal crystalline structure, the metal can be powdered easily. Bismuth is a good conductor of electricity, but a poor conductor of heat. When heated in air it is converted into the trioxide ( $\text{Bi}_2\text{O}_3$ ). The metal decomposes steam and combines directly with the halogens and with sulfur. Only the oxyacids attack metallic bismuth to form salts. Bismuth is usually present as an impurity in leads ores from which it is separated by an electrolytic process. All of the metallic bismuth produced in the United States is a by-product from the manufacture of electrolytic lead and copper.

### Industrial Uses

Pharmaceutical manufacturers used 36 per cent of the 1,592,000 pounds of bismuth consumed in the United States in 1951. Bismuth pharmaceutical products comprise principally anti-syphilitic drugs, indigestion remedies, and cosmetic powders. Metallurgical uses accounted for most of the remainder. The commercial bismuth alloys have low melting points and tend to expand on solidification. These properties make them especially useful as a support for thin-walled tubing to prevent wrinkles or collapse while being formed; to hold parts in dies or machine tools; to liquid-seal nitriding furnaces; and in ammunition and substitute solders. Additions of small quantities of bismuth or bismuth-lead to aluminum alloys, to steels (stainless, manganese, and carbon), and some other alloys result in marked increases

in machineability. Estimated world production of bismuth in 1951 was about 3,520,000 pounds. The main producers were the United States, Peru, Canada, and Mexico.

### Toxicity

The ordinary basic bismuth salts are practically insoluble in water and sparingly soluble in tissue fluids. Because of their fineness, insolubility, and density, these bismuth compounds adhere to mucous surfaces and inflamed areas and are used to furnish mechanical protection for ulcers, burns, and fistulas. A small amount of bismuth goes into solution and exerts a mild astringent and antiseptic action. These properties make the insoluble basic carbonate and nitrate helpful in the treatment of diarrhea, gastritis, and hyperacidity (1).

For many years extensive use has been made of bismuth compounds in the treatment of syphilis. Intravenous injection of water-soluble bismuth compounds is not used clinically because of the relatively high toxicity which has been shown experimentally and confirmed in the few clinical trials that have been reported. Clinical injections of "insoluble" bismuth tend to produce some diuretic effect analogous to that of mercury but generally not so marked. Peters (2) points out the similarity between the pharmacologic and toxic behaviour of lead and bismuth. Bismuth like lead may be liberated from tissue deposits during acidosis. Serious and sometimes fatal poisoning may occur with the injection of large doses into closed cavities and with extensive application to burns. Toxic manifestations and deaths following the intramuscular and rectal administration of the bismuth salt of hepta-diene-carboxylic acid (diallylacetic acid) in the treatment of infections of the upper part of the respiratory tract have been ascribed not to the bismuth part of the molecule, but to the hepta-dienecarboxylic acid or a contaminant thereof which may have been the hepato-toxin responsible for these deaths (3). Death of animals from bismuth nephritis following injection of soluble bismuth salts occurs within several hours to 24 days, the time being generally inversely proportional to the dose. The fatal dose by intra-



muscular injection appears to be of the order of 5 to 10 times higher than that by slow intravenous injection, for rabbits (4). In animals renal injury requires doses equivalent to more than nine times those used in human therapy (5). In man, the therapeutic dosage may produce foul breath, black line at the alveolar margin, and sometimes black spots on the buccal mucosa and throat, and annoying, but not serious stomatitis. It is stated that the administration of bismuth should be stopped when gingivitis appears for, otherwise, serious ulcerative stomatitis is likely to result, and other toxic effects may develop, such as malaise, albuminuria, diarrhea, skin reactions, and sometimes serious exfoliative dermatitis (3). A survey of 121 cases treated for syphilis demonstrates that 10.3 per cent were affected with bismuth hepatitis (6).

### Analysis

Moeller (7) has developed a method for the determination of bismuth which depends upon the spectrophotometric examination of chloroform solutions of the bismuth derivative of 8-hydroxyquinoline and which is applicable even in the presence of certain other metals providing they are not present in too large amounts. When less than 10 micrograms of bismuth is to be determined, Sandell (8) recommends the dithizone method. Even 1 microgram of bismuth can be determined by this method with fair accuracy. A rapid and specific method for the estimation of bismuth in body fluid is based on the deposition of the bismuth on a copper wire spiral with the nephelometric estimation of the redissolved bismuth by the quinine-potassium iodide test (9). Sensitive arc lines for the spectrographic identification of bismuth are 3067.7, 3024.6, 2938.3, and 2898.0.

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## BORON

### Characteristics

Boron, B, is a nonmetal, atomic weight 10.82, melting point 2300° C., boiling point 2550° C., and density 2.4. Boron forms the oxide, B<sub>2</sub>O<sub>3</sub>, and there is evidence of suboxides, BO and B<sub>3</sub>O. The sesquioxide may be prepared by heating boric acid to red heat. Boron oxide shows only faint basic properties and is in effect acidic although boric acid is a very weak acid. The addition of strong acids to borates liberates the weak boric acid, and this crystallizes from the water solution as the *ortho*-acid, H<sub>3</sub>BO<sub>3</sub>. The solubility of this acid increases markedly with temperature, as a saturated solution contains 2.6 per cent at 0° C. and 28.7 per cent at 100° C. The acid is somewhat volatile from hot solutions, possibly due to the formation of volatile hydrates (1). A native sodium tetraborate is found in California, Nevada, Oregon, and Asia Minor, and borax (Na<sub>2</sub>B<sub>4</sub>O<sub>7</sub>·10H<sub>2</sub>O) is prepared from these naturally occurring borates. Mineral borax was originally obtained from a salt lake in Tibet and sent to Europe under the name of "Tinkal." From an industrial viewpoint, borax is the most important of all boron compounds.

### Industrial Uses

The use of a minute amount of boron added to steel by means of ferro-alloys known as special addition, or "needling," agents or as intensifiers increases the hardness and improves the mechanical properties of steel in the quenched and drawn states.



About 0.003 per cent boron in steel appears to be the optimum amount. Production of boron-treated steels has been growing rapidly and interest continued unabated during 1951. It was estimated that by the end of the year as much as 15 to 20 per cent of the alloy steel produced in the United States contained boron (2). Boron has a strong tendency to absorb neutrons and this characteristic makes boron steel useful in controlling the operating rate of the uranium-graphite piles used to produce the new element, plutonium. Boron trifluoride ( $\text{BF}_3$ ) is also used in instruments employed for measuring neutron intensity in the piles. Amorphous boron of 82 to 86 per cent boron purity is now quoted at 11 dollars a pound in 100 pound lots or over. The so-called boron carbide,  $\text{B}_4\text{C}$ , has recently attained commercial importance because of its great hardness. It is prepared by the reduction of boric acid with carbon in the electric arc furnace. Boric acid is used in medicine, under the name "boracic acid," as a mild antiseptic. Probably the principal uses are as a lavage for the eye, for irrigating body cavities, and in boric acid ointment as an antiseptic and bland preparation for the treatment of burns. The easy solubility of borax in water forming a mildly alkaline and antiseptic solution, its low melting point, and its excellent fluxing properties make it one of the most useful of salts. Many articles of everyday life require borax in their manufacture. Borax fuses to form a glass which, since it contains an excess of acid oxide, is capable of dissolving metal oxides. Upon this property depends its use in soldering and welding to clean the metal surface of castings of oxide. Many oxides dissolved in fused borax impart characteristic colors (the familiar borax bead test). The colored glass finds use as artificial gems, and when ground, as pigment. Borax is used in the manufacture of glass, enamels, soap, and sizing for paper, and as a preservative for wood and meats. The production of boron minerals in the United States in 1951 amounted to 862,797 short tons, while the apparent consumption in that year was 650,000 short tons of boron minerals and compounds (2).

## Toxicity

Search of the medical literature reveals many instances of accidental poisoning with boric acid—cases of poisoning due to oral ingestion of borates or boric acid and cases presumably due to absorption of boric acid from wounds and burns (3, 4). The fatal dose of orally ingested boric acid in an adult is somewhat more than 15 to 20 grams and in an infant 5 to 6 grams (5). The symptoms which may be encountered in poisoning are depression of the circulation, persistent vomiting and diarrhea, followed by profound shock and coma. The temperature is subnormal and most observers describe a scarletina-form rash, which may cover the entire body.

Pfeiffer and his associates (4) have investigated the toxicity of boric acid and have shown that there is a significant absorption of boric acid when applied as a 10 per cent ointment to large areas from which the skin has been removed or to large areas of burned skin. However, the U.S. Food and Drug Administration state that there is no hazard in the use of talcum powders with 5 per cent of boric acid powder and that these preparations may safely be used as dusting powders for babies.

The boron hydrides—diborane, pentaborane and decaborane—are highly toxic and present a serious health hazard in manufacture and use (6, 7, 8). Svirbely (9, 10) has recently investigated the acute and subacute toxicity of pentaborane and decaborane vapors and found that an accumulated toxic effect apparently follows repeated subacute exposures in animals. Typical  $\text{LD}_{50}$  values for rats were 17.8 parts per million and for mice 10.9 parts per million following 4 hours of exposure. Detoxification of these boron hydrides within the body apparently does not readily occur.

## Analysis

Boric acid develops colors with alizarin S, quinalizarin, and the sodium salt of *p*-nitrobenzene-azo-chromo-tropic-acid. Fluorides and oxidizing substances in general interfere and must be eliminated for quantitative evaluation. The quinalizarin is perhaps the

most sensitive colorimetric agent for boric acid. A trace of boric acid changes the color from violet to blue. It is important to note, however, that commercial samples of hydroxyanthraquinone occasionally contain traces of boric acid, and that a purified grade of quinalizarin is necessary. A familiar test for boric acid, which is frequently applied, depends upon the formation of a volatile ether with methyl and ethyl alcohols, the vapor of which when ignited yields a green colored flame. The titration of boric acid in the presence of glycerol (11) or mannitol (12) is useful for the determination of larger amounts of boric acid. The National Bureau of Standards has reported new spectrographic methods for the determination of boron in steel which will determine one part of boron in a million parts of steel (13).

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## BROMINE

### Characteristics and Industrial Uses

Bromine, Br, atomic weight 79.92, liquid density 3.19 at 0° C., melting point -7.3° C., boiling point 58.8° C., is a reddish-brown liquid with fumes of the same color. Gaseous bromine has a density of 5.524 (air = 1). Bromine is found mainly as the bromides of alkali metals, in natural waters, brines, and sea water. Commercially it is recovered from brines and sea water. Liquid bromine is used as a reagent, an oxidizing agent, in organic synthesis, and in the manufacture of poison gas. A large portion of American-made bromine is consumed in an intermediary step in the manufacture of lead-tetraethyl. Pharmaceutically bromides are used as nerve depressants for sedative effects. Bromine production in the United States during 1951 amounted to 129,563,000 pounds.

### Toxicity

The physiological action of bromine is essentially the same as that of chlorine. It is a strong irritant to the upper respiratory passages and the lungs. Following the breathing of small amounts, there is an increased secretion from mucous surfaces, nosebleed, vertigo, and headache. After several hours' exposure there is nausea and epigastric pain, while after exposure to larger amounts there is brownish discoloration of the tongue and mucous surfaces, characteristic odor of the breath, bronchitis, and bronchial asthma, all of which may be followed by more severe symptoms. Like chlorine, the maximum concentration allowable for short exposure (1/2 to 1 hour) is 4 parts per million; the concentration dangerous for short exposure 40 to 60 parts per million, and the concentration rapidly fatal for short exposure is 1000 parts per million (1). The symptoms of poisoning from overdoses of bromides as nerve depressants are mental confusion, stupor, delusions, headache, nervousness, weakness, and sometimes a skin rash (2). Large doses cause exhaustion and cardiac failure. Bromine is very corrosive to



the skin and causes burns of a deep and penetrating nature, followed by ulceration which is persistent and difficult to heal. In cases where bromine has been accidentally spilled on the skin, the area should be promptly washed and treated with a paste of sodium bicarbonate.

### Analysis

Bromine may be separated from a number of other substances following its oxidation to the elemental form by either distillation or extraction from aqueous solution by means of any one of a number of solvents. A number of colorimetric procedures have been devised for the determination of small amounts of bromine. A color, for instance, is developed with Schiff's reagent (3); bromine forms a violet color in a sulfuric acid solution of basic fuchsin (4); eosin is formed by the interaction of bromine and fluorescein and may be used as a quantitative measure of the amount of bromine present (5). Phenol red similarly absorbs small quantities of bromine to form an indicator of the bromphenol blue type which is suitable for colorimetric determination (6).

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## CADMIUM

### Characteristics

Cadmium is a silver-white, bluish-tinged, lustrous metal, sufficiently soft to be cut with a knife. Its atomic weight is 112.41; melting point 320.9° C.; boiling point 767° C.; and density 8.6. The solubility of cadmium hydroxide,  $\text{Cd}(\text{OH})_2$ , in water at 25° C. is  $1.75 \times 10^{-3}$  grams of the anhydrous sub-

stance per 1 liter of solution. The metal is much more ductile and malleable than zinc and is capable of taking a high polish. When heated in air, cadmium volatilizes and burns with a bright flame emitting an abundance of brown fumes of cadmium oxide. Cadmium is readily soluble in dilute hydrochloric acid, slowly soluble in hot hydrochloric acid, and is almost unattacked by cold sulfuric acid. Unlike zinc, cadmium does not dissolve in alkali. Cadmium hydroxide is more soluble and more basic than zinc hydroxide and is soluble in ammonium hydroxide and in cyanides with the formation of the complex ions  $\text{Cd}(\text{NH}_3)_4^{++}$  and  $\text{Cd}(\text{CN})_4^{--}$ .

### Industrial Uses

Cadmium is principally used for the protective coating of steel and, to a much lesser extent, of copper and other alloys. The production of cadmium metal, or in pounds of contained cadmium, for 1953 was 9,837,197 pounds and the apparent consumption in the United States increased from 9,007,577 pounds in 1952 to 9,627,000 pounds in 1953. Cadmium is used in certain bearing alloys for automotive engines, aircraft, and marine engines. These bearings are stronger than babbitt and have superior embeddability and ease of bonding. Together with either silver or lead and tin, cadmium has been used in solders. When added to the extent of 1 per cent to copper, it forms an alloy which improves strength and wear resistance without seriously reducing the electrical conductivity of such material as trolley wire. About 0.4 per cent of cadmium is added to some type metals in order to improve the casting properties of the alloy. Smaller amounts of cadmium are used in pigments and in chemicals.

### Toxicity

In spite of the increased attention which has been devoted to the hygienic significance of cadmium, cases of poisoning, usually of unsuspected origin, appear with sufficient frequency to re-emphasize the fact that cadmium is a potentially dangerous substance. The careless use of cadmium-coated vessels as food or beverage containers has caused numerous cases of cadmium poisoning, the



majority of which have occurred since January 1941. Prior to this date, only 20 cases of cadmium poisoning due to the ingestion of cadmium had been reported in the literature. However, a large number of cases of cadmium poisoning from contaminated food or drink has since been reported; for example, Frant and Kleeman, 1941 (1), 50 cases; Cangelosi, 1941 (2), 208 cases; Schiffner and Mahler, 1943 (3), 7 cases; Jenner and Cunningham, 1944 (4), 62 cases; Lufkin and Hodges, 1944 (5), 12 cases; Garber, 1946 (6), 50 cases; Musso, 1946 (7), 300 cases. There were reported therefore a total of at least 689 cases of cadmium poisoning by ingestion within the 5-year period 1941 to 1946. Doubtless many other cases occurred but were not of sufficient severity to be reported. For instance, an outbreak believed to be due to cadmium poisoning in 1944 incapacitated 70 per cent of the personnel aboard a destroyer (8).

The symptoms of cadmium poisoning produced by ingestion are as follows: increased salivation, choking attacks, persistent vomiting, abdominal pain, diarrhea, and tenesmus (9). The significant feature of cadmium poisoning by mouth is the rapidity of physiological response. Usually individuals are affected within 15 to 30 minutes after ingestion of food or drink containing toxic quantities of cadmium. This in itself should be suggestive in cases of so-called food poisoning. However, occasionally symptoms may be delayed as long as 4 or 5 hours.

Occupational hazards with reference to cadmium are encountered in the smelting of ores and the manufacturing of alloys, in the spraying of metallic cadmium or pigments, in the heating of cadmium-coated iron and steel products, in the welding of cadmium-coated articles, and from the accidental ignition of cadmium dust or of molten cadmium. The increased use of cadmium in industry has largely resulted from its use in electroplating. Somewhat parallel with this increase, there has been an increased amount of poisoning. In general, the latter has not been primarily due to the electroplating process, but to the subsequent firing or welding of cadmium-plated material or the over-heating and oxidation of cadmium

metal. The extensive report of Spolyar and his associates (10) on cases of cadmium poisoning resulting from flanging operations on cadmium-plated pipe gives a particularly clear insight into the type of danger resulting from exposure to cadmium oxide fumes. Five cases are summarized, including one death. The mortality rate of industrial cadmium poisoning on the basis of the 59 cases reported in the literature appears to be 15 per cent. Ross (11) has recently cited a case of mass poisoning due to cadmium oxide fumes in which 23 individuals were affected. Finely divided cadmium dust from a cadmium recovery chamber became ignited due to red-hot cigarette ash carelessly dropped by one of the workers. The cadmium dust became incandescent in a few minutes emitting clouds of cadmium oxide fumes. Although no fatality occurred, incapacity was somewhat serious in some of the cases, disability amounting to as much as 2 months in one case. In the 14 cases recently reported by Shiels and Robertson (12) cadmium poisoning occurred as a result of inhalation of fumes arising from fire in a machine shop. A characteristic often reported with reference to the effects of exposure to cadmium oxide fume is that of delayed action. The effects usually appear 3 or 4 hours after exposure.

Most often fatalities from cadmium poisoning have resulted from inhalation of the fumes of cadmium oxide rather than the ingestion of cadmium salts. The first symptoms of industrial cadmium poisoning are usually dryness of the throat, cough, headache, vomiting, and a sense of constriction of the chest. The later symptoms are referable principally to the respiratory system and are characterized by cough, pain in the chest, severe dysphoria, and prostration. These symptoms result from a pneumonitis which in many instances is followed by bronchopneumonia. Unfortunately, cadmium oxide fumes have no pronounced odor nor immediate irritant effect and can be breathed in fatal concentrations without enough discomfort to drive the worker away from the exposure. A total of 11 deaths due to inhalation of cadmium fumes have occurred up to 1946. Barrett and his associates (13) have

made an extensive investigation of the physiological effects of exposure to cadmium and have determined the LD<sub>50</sub> dose for a number of species of animals and the type of pathological effect produced by such exposure. They estimate that the lethal dose of thermally generated cadmium oxide for man is probably not over 2,900 minutes per milligram per cubic meter. Doses considerably less than this caused incapacitation of all men who were exposed to it in an accidental exposure in a Canadian plant. The pathological findings in experimental animals which have been exposed to inhalation doses of cadmium oxide or cadmium chloride are confined to the lungs. Harrison and his associates (14) have determined the lethal concentration of cadmium chloride mist for dogs and have investigated the lung pathology produced by this substance. Princi (15) has investigated the effects of continued exposure of workers to cadmium dusts and fumes and has found no evidence of chronic poisoning. Some of the average atmospheric concentrations were found to be as high as 31.3 milligrams of cadmium per cubic meter of air. The most characteristic finding was a yellow ring on the teeth of the men who had had long exposure. Continuously exposed individuals having a blood cadmium concentration below 0.040 milligram per 100 grams of blood and a urinary cadmium concentration below 0.10 milligram per liter showed no apparent clinical abnormalities. These investigators suggest that cadmium may not be as great an industrial hazard as has previously been reported. As a result of cases of cadmium poisoning arising from the heating of cadmium coated metal with the attendant formation and volatilization of dangerous quantities of cadmium oxide, there has been agitation for the labelling of cadmium coated metals. While this is effective for large pieces, it is somewhat difficult to control as a means of protection when small objects are so coated.

Cadmium oxide dust is not apparently as hazardous as cadmium oxide fume. Princi and Geever (16) in a study of 30 dogs exposed for 1 year to either cadmium oxide dust or to cadmium sulfide dust found no observable physiological change in the ani-

mals in that time, nor any demonstrable pathological changes in the lungs, livers and kidneys. Furthermore cadmium levels as high as 0.22 milligrams per 100 grams of blood and 0.357 milligram per liter of urine were unaccompanied by any evidence of damage. Gabby (17) found no evidence of damage following the oral administration of cadmium sulfide and cadmium selenide to rats. The only effect noted was a slight taste aversion when the diet contained more than 1 per cent of the compound. However, Friberg (18) has noted the occurrence of proteinuria among workers exposed to cadmium dust and is inclined to attribute the proteinuria to cadmium. Potts *et al.* (19) have investigated the tissue distribution of cadmium following inhalation using cadmium 115 as a tracer. Cotter and Cotter (20) have stressed the importance of studying the blood chemistry in cases of cadmium poisoning.

### Analysis

The analytical methods for cadmium commonly used are based on colorimetric comparison with known amounts or by suitable dropping mercury electrode procedure. The colorimetric sulfide method with ultraviolet ray intensification has a sensitivity of 1:2,500,000 and may be applied to the analysis of fume or dust, as well as to biological material (21). Cadmium may also be detected and estimated by Setterlind's method using dithizone (22, 28), by cadion (23) (sensitivity 1:300,000,000), or by  $\beta$ -naphthoquinoline (24) (sensitivity 1:500,000). While the sensitivity of tests by these organic reagents is reputed to be high, many substances interfere and care should be employed in checking for the presence or absence of cadmium by any of these reagents. Feicht and his associates (25) have developed a procedure for the quantitative evaluation of small amounts of cadmium with a lower limit for the reliable determination of this element lying between 0.025 and 0.05 milligram of cadmium. Boudene and Truhaut (26) have recently described a nephelometric method based upon the precipitation of brucine iodocadmiate. Thiers and his associates (27) have shown that, while very fine



particulate cadmium oxide dust is practically invisible in lung sections under the microscope, the particles may be revealed by subjecting unfixed sections of lung tissue to the vapor of 8-hydroxyquinoline. The particulate cadmium oxide is converted to cadmium 8-hydroxyquinolate dihydrate which fluoresces intensely green under ultraviolet light. A field method for detection of cadmium coating on metal is that of Goldstone which depends on formation of the readily distinguishable canary yellow color of cadmium sulfide (3). The distinctive lines for the spectrographic detection of cadmium are 3610.5, 3466.2, 3261.1, and 2288.0.

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#### CERIUM

##### Characteristics

Cerium, Ce, resembles iron in color and luster but is only a little harder than lead. It is somewhat malleable and ductile and takes a good polish. It has a density of 6.8, melting point 640° C., and boiling point of 1400° C. It oxidizes in moist air, burns in air like magnesium, and is insoluble in water, but is readily soluble in acids. Cerium is the most abundant and the most easily extracted of the rare-earth metals. It is found in cerite, allanite, and in monazite sand. The latter contains about 30 per cent of cerium oxide,

26 per cent phosphorus pentoxide, 16 per cent lanthanum oxide, 10 per cent neodymium oxide, and 8 per cent of thorium oxide (1). An alloy of the metals of the cerium group obtained from this sand is called mischmetal or commercially "cerium", and is used for manufacturing ferro-cerium. Cerium forms two well-defined series of salts in which it has valences of 3 and 4, respectively.

### Industrial Uses

The pyrophoric ferro-alloy of cerium is the most widely used material for lighter flints, and is also used in tracer bullets and other pyrotechnics and as a getter in thermionic tubes. Cerium is used in aluminum and magnesium alloys to improve the mechanical properties of pistons and other aircraft parts and in the ceramic field as a component of certain types of glass. The use of cerium oxide as an abrasive for polishing prisms and lenses in optical equipment results in an almost perfect polish three times faster than the best rouge (2). Many common and precious metal-cerium master alloys are available. Cerium standard alloy is made up of 40 to 50 per cent cerium, 22 to 25 per cent lanthanum, 15 to 17 per cent neodymium, and small amounts of other metals. The Welsbach mantle for gas light consists of thoria ( $\text{ThO}_2$ ) and 1 or 2 per cent of ceria ( $\text{CeO}_2$ ). Monazite is used in the production of chemicals and also as a flux in whiteware bodies and glazes.

### Toxicity

Cerium resembles aluminum in pharmacological, as well as in chemical properties. The insoluble salts, such as the oxalate, are stated to be nontoxic even in large doses. Cerium oxalate is used to prevent the vomiting of pregnancy. The average dose is 0.05 to 0.5 gram (3). Lange (4) has reported 10 years' experience using "Peremesin", a cerium preparation for this purpose. However, Ozaki (5) found that cerium tartrate produced a direct injurious action on the hearts of small animals. The distribution of cerium in tissues and organs was determined by Provinciali (6). Absorption of cerium salts following oral administration is only slight and cerium is excreted exclusively by the

gastrointestinal tract. Oelkers (7) has recently found that cerium chloride acts directly on the smooth muscle of the intestines, producing loss of motility. The effect upon the nervous system of the rare-earth metals following inhalation may preclude to any large extent welding operations, during which these metals may be vaporized and inhaled by the worker (8). Cerium is stated to produce polycythemia but is useless in the treatment of anemia owing to its toxic effects. The salts increase the blood coagulation rate. However, according to Meyer (9), cerium does not affect either the blood picture or the growth of animals, and, in general, has a low toxicity rating. These effects are contrary to those found by Bamann (10) on intravenous injection of the salts of cerium. He states that these substances block the normal metabolic pathways and interfere with blood coagulation by reducing the prothrombin content of the blood.

### Analysis

Most reagents which develop a color with cerium, such as benzidine hydrochloride, methylene blue, and sodium arsanilate, are not specific for this element, and interfering substances which are sometimes difficult to separate must be removed before cerium can be colorimetrically evaluated. However, it is stated that the color which develops with tannic acid in 50 per cent glycerol solution in the presence of cerium is specific. The blue-violet color thus obtained is sufficiently intense for the detection of 8 micrograms of the metal (11). The spectral lines of special sensitivity for cerium are 4186.60, 4040.76, and 4012.40.

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## CHLORINE

### Characteristics

Chlorine, Cl, a halogen element of atomic weight 35.46, boiling point  $-34.7^{\circ}\text{C}$ ., melting point  $-102.1^{\circ}\text{C}$ ., density 2.488 (air = 1), is a greenish-yellow gas with a pungent, irritating odor. Chlorine, one of the most important industrial gases, is easily liquefied under pressure. The usual valence of chlorine is 1, but it can act with a valence of 3, 4, 5, and 7. Chlorine is not combustible in air, but reacts chemically with many common substances and may cause fire or explosion when in contact with them. Chlorine ranks twelfth among the elements in order of abundance. It occurs as chlorides (sea water, salt deposits), in many minerals, and in all plant and animal tissues. Chlorine is a secondary product in the manufacture of sodium hydroxide by electrolysis of sodium chloride.

### Industrial Uses

Liquid chlorine is used extensively to disinfect the water and sewage of cities, for recovering tin from scrap plate, for bleaching cotton, paper, and flour, and for the manufacture of disinfecting agents, such as chloride of lime and other chemicals. Chlorine readily enters into addition and substitution reactions with many types of organic compounds. With aromatic hydrocarbons, chlorine is widely used for the chlorination of both side chains and nucleus of the compound in the presence of the proper catalyst. Chlorine is also utilized in petroleum refining. It is handled commercially in the form of a liquid in steel cylinders or special tank cars and is manufactured, transported, and consumed in quantities of several thousand tons daily.

### Toxicity

Rodents exposed to chlorine gas show little initial excitement; early signs of irritation of eyes and nose and early and increasing signs of pulmonary edema occur. Except for terminal convulsions, there is comparatively little activity. Study of the organs at death has revealed edema and hemorrhage of the lungs (1). Toxic effects from chlorine gas usually result from accidental exposure to large volumes of gas in industry rather than continued exposure to small quantities. Chlorine is readily detected owing to its peculiar smell and irritating qualities. As a result of its strong oxidizing properties, it affects the mucous membranes, causing eye, nasal, and throat irritation, and on inhalation has a pronounced effect on the lung tissue. Usually exposure to chlorine gas in concentrations of 40 to 60 parts per million is followed by pneumonitis and edema of the lungs, and in a concentration of 1,000 parts per million it is invariably and rapidly fatal. Research by the U. S. Bureau of Mines (2) has shown that the least concentration to give detectable odor is 3.5 parts per million; to cause throat irritation, 15.1 parts per million; and to cause coughing, 30.2 parts per million. The maximum concentration allowable for prolonged exposure as given by Henderson and Haggard is 0.35 to 1.0 parts per million; the maximum concentration allowable for short exposure ( $\frac{1}{2}$  to 1 hour) is 4.0 parts per million (3).

### Analysis

Chlorine in small amounts may be determined colorimetrically by a number of organic reagents including benzidine with which it produces a green color, dimethyl-*p*-phenylenediamine hydrochloride (red color), resorufin (blue color), *o*-tolidine (yellow color). For the detection and estimation of chlorine as an aerial contaminant in concentrations as low as 0.01 part per million the *o*-tolidine method is preferable. Samples of air of known volume are drawn through a bubbler containing *o*-tolidine reagent until the depth of color produced is equal to that of one of a series of standards prepared from potassium dichromate solution (4). In determining residual chlorine in

water, it is sometimes advantageous to differentiate between free chlorine and chloramine. A colorimetric method based upon the specific reaction between free chlorine and methyl orange has recently been proposed for this purpose (5). Larger amounts of chlorine in aqueous solution may be determined by adding an excess of potassium iodide and titrating the free iodine with standard sodium thiosulfate solution.

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## CHLORINE DIOXIDE

### Characteristics

Chlorine dioxide, or chlorine peroxide,  $\text{ClO}_2$ , is a reddish-yellow gas prepared industrially usually by the interaction of chlorine and sodium chlorite. It has an unpleasant odor and decomposes in sunlight. Its density at  $11^\circ\text{C}$ . (air = 1) is 2.4 and its boiling point is  $9.9^\circ\text{C}$ . per 730 millimeters. The liquid substance is red and explosive. It melts at  $-76^\circ\text{C}$ . One liter of water dissolves 3.01 grams at  $25^\circ\text{C}$ . and 34.5 millimeters pressure of mercury. The aqueous solution undergoes hydrolysis to chlorous and chloric acids, and when warmed decomposes to form chlorine, oxygen, and chloric acid. The aqueous solution prepared at lower temperatures, i.e., at  $4^\circ\text{C}$ . contains about 20 times its volume of chlorine dioxide and when cooled still further a crystalline hydrate, possibly  $\text{ClO}_2 \cdot 8\text{H}_2\text{O}$ , separates out.

### Uses

Chlorine dioxide is a substance of increasing importance in industry. It is used as a bleaching agent and in the purification of water, particularly with reference to taste and odor control. It is used as a bleaching agent for flour, beeswax, and fats and oils, especially in tallow and fat-rendering plants.

### Toxicity

Owing to its instability chlorine dioxide is a dangerous substance and requires great care in handling. It is usually generated on the premises as needed. Care must be exercised to insure the absence of organic matter with which both sodium chlorite and chlorine dioxide react violently. Proper precautions for safeguarding against fire and explosions in the preparation and use of chlorine dioxide gas have been recommended by the National Board of Fire Underwriters (1). In addition to the danger of handling this substance because of its instability, chlorine dioxide is toxic and is more poisonous than chlorine, according to Petry (2). In a case described by this investigator a research worker was exposed on several occasions to an unknown amount of chlorine dioxide and suffered acute irritation of the respiratory passages which ultimately developed into chronic emphysema and bronchitis. In another case of poisoning from this gas an ocular muscular paralysis was noted. Petry considers that chlorine dioxide may have a specific action on the central nervous system.

### Analysis

Since chlorine dioxide is a powerful oxidizing substance, the colorimetric determination based upon its reaction with *o*-tolidine or with benzidine should be applicable for its determination as an atmospheric contaminant. However this method would not be specific in the case of chlorine dioxide-chlorine mixtures.

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## CHROMIUM

### Characteristics

Chromium, Cr, atomic weight 52.01, is a silver-white, hard, brittle metal with density 7.1, melting point 1615° C., and boiling point 2200° C. Chromium is oxidized only to a very slight extent by moist air at ordinary temperatures. The metal is slowly dissolved by mineral acids with the exception of nitric acid which induces a state of passivity, particularly when concentrated. The commercially important chromium compounds relate principally to the trivalent and hexavalent types of which the latter are, by far, the more important. Chromium initially appears in commerce in the form of chromite ore from which the alloy steels are directly prepared without intermediate reduction to chromium. Chromite also serves as the starting point in the preparation of chromates and chromium trioxide.

### Industrial Uses

In 1951, the consumption of chromite in the United States amounted to 1,212,480 tons (1). Industry recognizes three grades of chromite—metallurgical, refractory, and chemical. Ferrochrome, the product made from metallurgical ore, is used in alloy iron and steel where it increases hardenability, strength at high temperatures, and resistance to abrasion, corrosion, and oxidation. Chromium is an essential component of high-speed steel, many of the engineering steels, stainless steels, and a large proportion of other corrosion-resistant alloys. Chrome chemicals are used in the tanning of leathers for shoes, plating and anodizing of metals, production of catalysts used in gasoline and synthetic rubber manufacture, in the refractory industry, and in the manufacture of certain pigments. The General Electric Company has recently developed a chromium carbide with nickel as a binder (for use in extra hard cutting tools) which is said to contain no tungsten or cobalt (1). Air contaminated with chromic acid mist from chrome plating vats or with the dust

from chromates or dichromates is the principal type of exposure to chromium in industry which is of interest to the industrial hygienist.

### Toxicity

The toxic action of chromium is confined to the hexavalent compounds of chromium. Trivalent salts show none of this toxic effect. In the animal experiments of Akatsuka and Fairhall, cats which were given as much as 1,000 milligrams of chromic phosphate or chromic carbonate in their food per day or caused to inhale up to 200 milligrams of chromic carbonate over a period of 17 weeks, exhibited no sign of illness, loss of weight, or tissue damage (2). The growth of chromium plating and the increased household utilization of stainless steel has posed the question of the hygienic significance of chromium in food and drink. However, the chromium that is taken up from chrome steels or chromium-plated ware by food and water enters solution as a chromic salt and not as a chromate or a dichromate. The latter require powerful oxidizing agents for their formation. On the other hand, chromium plating exposes the worker to spray or mist and has given rise to much occupational ill health (3). Workmen are frequently afflicted with dermatitis (4), with perforation of the nasal septum and, where splashings of the liquid occur in contact with skin, abrasions with chrome ulcers or "chrome holes". A floating baffle of plastic chips has been suggested as a means of reducing the atmospheric concentration of chromic acid mist over chromium-plating tanks (5). Chromate dust in industry similarly causes injury to workers (6).

While systemic poisoning from chromates is rare, the unpleasant effects of exposure to chromic acid mist or to chromate dust where environmental control is inadequate (7) are likely to lead to a large labor turnover. A more recent type of industrial exposure to chromic acid mist occurs in anodizing operations, which is an operation in which a coating highly resistant to corrosion is formed on aluminum and its alloys through the anodic oxidation of the aluminum. Chromic acid is used as the solution in which

the anodizing operations are carried out and may attain a concentration as high as 10 per cent. The hydrogen liberated during the anodizing operation carries a significant amount of chromic acid mist along with it (8). Greenburg and his associates (9) have indicated a new source of chromate exposure with reference to spray painting. In a survey of 106 painters in a large airplane factory in New York State, five cases of perforated nasal septum were found which were attributed to the large amount of zinc chromate pigment present in the paint. Gross (10, 11) has reported several cases of lung cancer in Germany during the war in plants where workers were exposed to zinc chromate dust. Machle and Gregorius (12), after analysis of the mortality data of the chromate-producing industry in the United States, report a high death rate for cancer of the respiratory system among exposed employees; 21.8 per cent of all deaths were due to cancer of the respiratory system, 16 times the expected ratio. Further statistical studies in this country by Baetjer (13) and by Brinton and his associates (14) have also indicated a high cancer rate among chromate workers. However, Bidstrup (15), in a survey which involved mass radiography and clinical study of 724 workmen of the 765 employed in the chromate industry in Great Britain, found only one case of pulmonary carcinoma. Irritation due to chromates has been reported from contact with diesel locomotive radiator fluid (16). The dermatitis of cement workers has recently been traced to the small amount of chromium found in cement (17, 18, 19). Denton and his associates (20) found the water-soluble hexavalent chromium content of the first washing of cement to vary from 0.03 to 6.9 micrograms per gram of original cement. The exceedingly minute amount of chromium, if any, added to food prepared in stainless steel (nickel-chromium-iron) utensils is without hygienic significance (21).

### Analysis

Traces of chromium may be determined by means of diphenylcarbazide (2) which is an extremely sensitive reagent making it possible to detect the presence of 1 part of

chromium in 20 million parts of the solution (22). For the determination of chromic acid mist, air samples are drawn through an impinger apparatus containing normal sodium hydroxide and the chromium content measured by the addition of potassium iodide, acidifying with hydrochloric acid and titrating with 0.01 normal sodium thiosulfate (3).

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## COBALT

### Characteristics

Cobalt, Co, is a silver-white metal with a slate-blue tinge, having an atomic weight of 58.94, a density of 8.9227 at 19° C., melting point 1490° C., boiling point 2900° C., and hardness 5.6 on Moh's scale. Cobalt exists in two allotropic forms,  $\alpha$ -cobalt, hexagonal, stable below 400° C. and  $\beta$ -cobalt, cubic, stable above 400° C. Unlike iron, cobalt is not attacked by air and water at ordinary temperatures, but it is superficially oxidized at a red heat. Cobalt is characterized by its black sulfide, which is insoluble in acetic and dilute hydrochloric acids, and by the fine blue color which its compounds impart to various salts on fusion.

### Industrial Uses

The total amount of cobalt consumed in the United State for all purposes in 1951 was 9,932,993 pounds. By far the greatest amount of cobalt is used in stellite and stellite-type alloys and in carbide-type alloys, all of which totaled 49 percent of the total amount consumed in 1951. Cobalt is used as the bonding material in the manufacture of cemented tungsten carbide and this constitutes one of the most important uses of the metal at the present time. Ce-

mented tungsten carbide tool and die fabrication has become a key industry and is rapidly displacing steel cutting tools for many purposes in the metal industry because of the hardness and wear resistance of this material. A large quantity of cobalt (1,322,097 pounds in 1944) was used in magnets of the "Alnico" (aluminum, nickel, and cobalt) type. These are far more powerful than any type of steel magnet. Smaller amounts were used in high-speed steel and for certain nonmetallic purposes, such as ground-coat frit and pigments. The use of cobalt in bright plating is increasing rapidly. Cobalt oxide is a very efficient catalyst for the oxidation of ammonia, and cobalt-thorium catalysts are employed in the Fischer-Tropsch process for the synthetic production of gasoline from coal. A certain amount of cobalt is used in soil dressings in areas where cobalt deficiency has produced such diseases in sheep and cattle as "bush sickness", "salt sickness", or "enzootic marasmus". Cobalt trifluoride,  $\text{CoF}_3$ , which readily gives up 1 atom of fluorine, and therefore acts as a fluorine carrier, is finding extensive use at the present time in the fluorination of hydrocarbons.

### Toxicity

The toxic action of cobalt by mouth is low. Chittenden and Norris in 1887 observed that the poisonous action on rabbits is slow and apparent only after the administration of relatively large doses. Intravenously, cobalt has been observed to cause paralysis of the extremities, enteritis, and death. Cobalt naturally occurring in foodstuffs is for the greater part unabsorbed and is excreted in the feces (1), while injected cobalt is excreted in the urine. Copp and Greenberg (2), using radioactive cobalt, found that over 60 per cent of the cobalt given by stomach tube was recoverable in the feces. The latter investigators also found that the amounts distributed in the tissues following the injection of cobalt are very small, the highest concentrations being present in the glandular organs, such as the pancreas, liver, spleen, and kidney, and in the bones. They also found that injected cobalt in animals was quickly eliminated—a finding that could

not be substantiated by Kent and McCance in man.

Powdered cobalt has been shown to produce dermatitis (Schwartz *et al.*, 3). Stewart (4) has shown with a patient sensitive to cobalt and nickel that hyperemic, edematous, vesicular lesions produced by cobalt were definite but that the sensitivity was somewhat less than to nickel. Haxthausen (5) has demonstrated experimentally a hypersensitivity of the skin to cobalt, while Rabeau and Ukrainczyk (6) have been unable to confirm the reciprocal hypersensitivity of nickel cases to cobalt and vice versa.

A well-recognized effect of the administration of cobalt salts to animals is that of the production of a definite polycythemia and most of the investigations relating to the physiological activity of cobalt have revolved around this phenomenon. Orten (7) concluded that the hematopoietic activity of cobalt is the result of an increase in rate of formation of hemoglobin and erythrocytes rather than a passive accumulation of red cells resulting from a diminished rate of cell destruction. In histologic studies to evaluate the toxicity of cobalt, Hopps and his associates (8) found that dosage of rats with cobaltous chloride in amounts 10 times the human dosage produced no significant degenerative changes in parenchymal organs as evidence of toxicity. Frequent reference has been made to work of Barron and Barron (9), who state that small amounts of cobalt inhibit the respiration *in vitro* of various tissues, notably reticulocytes and bone marrow. However, the recent experiments of Warren and his associates (10) have been unable to confirm this finding. Frost and his associates (11) found a definite hematopoietic response at a minimum level of 1 milligram per kilogram of body weight per day when cobalt was added to iron and copper in the diet. Scott and Reilly (12) find that cobaltous chloride has no effect on iodine metabolism or thyroid activity.

It has been stated by Griffith and others (13), that cysteine has a detoxifying action in cobalt poisoning. Poisoning from cobalt according to these investigators may be due to fixation and loss of sulfhydryl compounds

in tissues with resulting interference with the oxidative mechanism. More recently Grant (14) has found that by supplementing the diet of rats with methionine it is possible to abolish both weight loss and polycythemia induced by cobaltous chloride. Cobalt has been shown to produce polycythemia in rats, rabbits, ducks, and in dogs. Fredrick and Bradley (15) found the LD<sub>50</sub> dose of cobalt metal powder to be 10 to 20 milligrams per 100 grams of body weight following intraperitoneal injection of white rats. It is of interest in this connection that Harding (16) found cobalt metal powder to be 500 times more soluble in plasma than in saline. No threshold limit has been established for cobalt.

In a survey of the cemented tungsten carbide industry, where workers are exposed to a certain amount of cobalt metal dust, Fairhall *et al.* (17, 18) found that the health condition of the employees as a whole does not appear to differ from that in other industries investigated by the Public Health Service, except in frequency of findings with respect to the conjunctivas and upper respiratory tract.

### Analysis

Satisfactory confirmatory tests for the identification of cobalt usually require the removal of a number of interfering substances.  $\alpha$ -Nitroso- $\beta$ -naphthol and certain sulfonic acids derived from this substance give colors with small amounts of cobalt in dilute solution. It is stated that both  $\alpha$ -nitroso- $\beta$ -naphthol and  $\beta$ -nitroso- $\alpha$ -naphthol will detect minute amounts of cobalt (19), although the latter is somewhat more sensitive. Small amounts of cobalt give a red color with nitroso-R-salt (1-nitroso-2-hydroxynaphthalene-3,6-disulfonate of sodium), which is stable towards hot 30 per cent nitric acid that discharges the colors produced by other metals. For the determination of quantities of cobalt of less than 0.05 milligram, the nitroso-R-salt method of McNaught (20) may be used. The further modified method of Young, Pinkney, and Dick (21) is applicable for determinations ranging from 0.01 to 0.50 milligram of cobalt. DeGray and Rittershausen (22) have



developed a method which depends upon the color produced by the ammoniacal ferricyanide procedure. This method permits determination of cobalt with a precision of 0.06 milligram of cobalt. Very small amounts of cobalt in biological materials may be determined with accuracy by means of *o*-nitrosocresol (1-methyl-3-hydroxy-4-nitrosobenzene) (23). Keenan and Flick (24) have developed a method for the determination of minute amounts of cobalt in atmospheric dust samples which is sensitive and accurate for air samples containing 0.1 milligram of cobalt or more. Saltzman (25), using 1-nitroso-2-naphthol for extraction of the cobalt, has applied the nitroso-R salt method to biological material with good recovery in microgram amounts. The sensitive spectral arc lines for cobalt are 3453.51, 3405.12, and 2407.26. Keenan and Kopp (26) have recently developed a spectrochemical method of great accuracy for the determination of minute quantities of cobalt in animal tissues.

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#### COLUMBIUM

##### Characteristics

Columbium, Cb (formerly referred to as niobium, Nb), is a steel-gray metal with bright metallic luster, having a density of 8.4 and melting point of 1950° C. It forms two series of compounds of valence 3 and valence 5. The similarity of chemical behavior of columbium and tantalum makes the quantitative separation of the two somewhat difficult. The metallic columbium may be prepared by reduction of the oxide with metallic calcium or aluminum and at the

temperature of the electric furnace the oxide may be decomposed to the metal by heating in a vacuum. The metal does not tarnish readily and although it is very hard, it may be rolled or hammered or drawn into wire (1, 2, 3).

### Industrial Uses

Until very recently, columbium had no significant technical application. However, it has become important in certain alloy steels and because of the great corrosion resistance and high melting point, it is used in gas turbines, turbosuperchargers, and in jet-propelled airplanes where materials are subjected to terrific pressure and heat. An important use of columbium is to inhibit intergranular corrosion in chrome-nickel steel by preventing formation of chromium carbide. It is also used in rods of welding stainless steels. The consumption of columbium ore in the United States in 1945 was 4,278,301 pounds of which only 1,149 pounds was produced in the United States. Columbium sheet metal was priced at 500 dollars a kilogram in 1945. Columbium forms a carbide which is extremely hard and which imparts such unique properties to cemented tungsten carbide cutting tools that, in spite of the expense of columbium, it has attained commercial importance in this field. Owing to the defense situation recent specific data regarding the production and consumption of columbium are not available. In 1951 columbium was placed under defense allocation by the National Production Authority and columbium-bearing steels have been reserved for defense needs.

### Toxicity

Because of its increasing industrial importance, frequent inquiry has arisen with reference to the possible toxicity of columbium. Since columbium occurs and is immediately adjacent to vanadium in Group V and because of the toxicity of vanadium, it might be anticipated that columbium would also possess toxic properties. Recent experimental studies with columbium and other rare earth metals by Cochran and his associates (4) have shown that both potassium columbate and columbium chloride are quite

toxic to rats when administered intraperitoneally. Columbium also showed a pronounced inhibitory effect towards adenosine triphosphate.

### Analysis

Neither the separation nor the identification of columbium is simple. Columbium has such similar properties to those of tantalum that most processes of separation are more or less methods of approximation. One of the most useful methods of separation depends upon the solubilities of the double fluorides of columbium and tantalum,  $K_2CbF_7$  and  $K_2TaF_7$ . Partial separation of columbium from tantalum can be effected by treating the freshly precipitated hydrated oxides with a mixture of hydrogen peroxide and hydrochloric acid, in which the columbium dissolves readily, while the tantalum dissolves only sparingly. Gravimetric estimations of columbium may be made by utilizing the reagent 8-hydroxyquinoline (5). Pyrogallol and resorcinol have also been proposed as reagents for the determination of columbium. Sodium hypophosphite forms insoluble complex compounds with tantalum and columbium in the presence of tartaric or citric acid. The precipitate with tantalum occurs only in the presence of ammonium oxalate. The reaction is specific and applicable to concentrations of 1:1,000,000 (6).

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## COPPER

### Characteristics

Copper, Cu, atomic weight 63.57, density 8.92, melting point 1083° C., boiling point about 2310° C., is a reddish colored ductile



metal. Its tenacity is next to iron, although a copper wire will support only half of the weight borne by an iron wire of the same size. As a conductor of heat it is surpassed by gold and silver, and it is next to silver as a conductor of electricity. The presence of a few tenths per cent of certain impurities, however, especially arsenic, greatly increases the electrical resistance. Copper forms two series of compounds, cuprous and cupric, of which the latter are more stable. Both cupric and cuprous ions form complex ions, many of which are stable. The alloys of copper are manifold and have a great variety of applications. Of these, the brasses and bronzes are especially important.

### Industrial Uses

Metallic copper is one of the most important of all metals. For a great variety of technical and domestic purposes, copper is especially valuable for its toughness. Pure copper is of the greatest importance in the electrical industry, since it is an excellent conductor of electrical energy. During 1951, 1,303,000 short tons of new refined copper were consumed in the United States. While small quantities of impurities lower the conductivity to a very great extent, certain alloys, such as beryllium-copper, retain a large proportion of the conductivity of copper itself. Copper is used in insecticides and fungicides, in anti-fouling paints, and in copper naphthenate as a rot-proofing agent for fabrics. A recent method for the rot-proofing of fabrics consists of the fixation of the copper compound of dimethyl-glyoxime within the fabric. As determined by soil burial tests this treatment proved more effective than copper naphthenate for rot-proofing purposes.

### Toxicity

Attempts to induce chronic copper poisoning in rabbits by feeding have been unsuccessful, although there is evidence of a considerable amount of copper storage in the liver (1). Chronic intoxication is induced in sheep by daily quantities of 1.5 grams copper sulfate according to these investigators, the condition developing in periods of from 30 to 80 days. Clinical symptoms include

dullness, depression, and anorexia; post-mortem examination showed icterus, cirrhotic liver, and swollen and congested kidneys. The copper content of the liver and, to a lesser extent, the kidneys, is considerably increased but relatively little change occurs in that of the remaining soft tissues examined.

Copper seldom gives rise to poisoning, although its salts are somewhat irritant and corrosive. The salts have a harsh, metallic, astringent taste. In large amounts they give rise to violent vomiting and purging with intense pain in the abdomen and the usual symptoms of acute corrosive poisoning with collapse, weak pulse and respiration, delirium, coma, convulsions, and paralysis. The occurrence of chronic copper poisoning in man has not been established. The relation of copper to hemochromatosis was investigated by Mallory (2) and was considered to be due to long-continued ingestion of copper salts, but this has not been confirmed. However, it is thought by some that gastrointestinal catarrh or colic and diarrhea, which occasionally occurs in copper and brass workers, is due to copper swallowed or inhaled. Copper salts are relegated to a low position as a major poison, but minor disturbances, such as vomiting, are usually noted following ingestion. Exposure to copper dust, copper carbonate dust, or flaked copper has been known to give rise to intense sneezing, nausea, and weakness. Schiötz (3) describes seven cases of copper fever from a paint factory where red oxide of copper was being pulverized. Wallgren and Gorbатов (4) found serum copper in cases of metal fume fever in the copper industry to exceed 160 micrograms per 100 cubic centimeters of serum, which is definitely pathological. Copper has also been found in the urine in cases of exposure to finely divided copper or copper salts, suggesting that copper is a local irritant and excreted by the kidneys.

### Analysis

Methods applicable to the analytical determination of copper, which are chiefly of interest to the industrial hygienist, relate to the determination of copper as an aerial con-

taminant, such as airborne copper dust or the mist or spray from solutions of copper compounds. These amounts of copper are necessarily small and may be determined most conveniently by colorimetric procedures. In general, minute amounts of copper may be separated quantitatively by a sulfide procedure from a number of interfering substances. Diphenylthiocarbazone reagent is also useful in this type of separation. A large number of organic compounds give sensitive color reactions with copper, of which diphenylthiocarbazone (5) and sodium diethyldithiocarbamate may be particularly mentioned. Perhaps the most satisfactory reagent is sodium diethyldithiocarbamate (6). A slightly acid or ammoniacal cupric salt solution produces a brownish precipitate of the copper diethyldithiocarbamate which in very dilute solution is suitable for colorimetric comparison, especially in solutions stabilized with a protective colloid. The copper diethyldithiocarbamate may be extracted with carbon tetrachloride or isoamylacetate, in both of which the copper salt is rather stable. Comparison may be made with known quantities of copper for reference. Tetraethylenepentamine has recently been recommended as a colorimetric reagent for copper in the determination of larger quantities ranging up to 200 parts per million (7). The spectrographic identification of copper is especially convenient. The most intense and sensitive arc lines for this element are 3273.96 and 3247.55.

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## DECABORANE

### Characteristics

Decaborane, decaboron tetradecahydride,  $B_{10}H_{14}$ , is the only solid volatile hydride of boron. It melts at  $99.7^{\circ} C.$ , boils at  $213^{\circ} C.$ , and has a density of  $d_{99/4} 0.92$ . At room temperature the density is 0.94. Its vapor pressure at  $55^{\circ} C.$  is 0.3 millimeter (approximately), rising to 19.0 millimeters at  $100^{\circ} C.$  Decaborane is insoluble in water, but dissolves in alcohol, ether, benzene, and particularly in carbon disulfide, from which it crystallizes in long, feathery needles when enough of the solvent has been evaporated. Decaborane is best prepared, according to Stock (1) by heating diborane,  $B_2H_6$ , to  $115$  to  $120^{\circ} C.$  for 48 hours. Decaborane is easily identified and isolated from the other boron hydrides because its volatility is so low that there is no difficulty in removing the lower boiling hydrides, yet it is sufficiently high that it can be sublimed free from impurities. It has a characteristic, somewhat pungent, odor and slowly vaporizes at room temperature. When condensed it crystallizes in compact aggregates, but when slowly sublimed *in vacuo* it forms clear, transparent long needle-like crystals. It is quite stable, even on warming, but explodes when heated in oxygen. It hydrolyzes in water, slowly at room temperature but rapidly when heated. Decaborane reacts slowly with the halogens, dissolves readily in liquid ammonia and shows hardly any reaction with concentrated nitric acid. It dissolves in a solution of sodium hydroxide, forming a colorless solution that evolves hydrogen continuously.

### Toxicity

Svirbely (2) has investigated the acute toxicity of decaborane with rats, mice, dogs, and rabbits by various modes of administration. Listlessness, incoordination, tremors, convulsions, a comatose state and death were noted at the lower dosage levels, while convulsions were absent at higher concentrations. There was evidence of liver and kidney damage. With repeated small doses



Svirbely (3) found a cumulative toxic effect. Possible liver and kidney damage was indicated following oral administration and percutaneous application. Walton and his associates (4) noted a progressive decrease in heart force following the administration of decaborane to dogs. Complete protection against decaborane vapor may be obtained for many hours by the use of a conventional chemical cartridge respirator filled with silica gel (Hill and Svirbely, 5). Activated carbon is about half as effective.

### Analysis

According to Stock (6) the odor and green coloration they impart to a flame are sensitive qualitative tests for the hydrides of boron. The hydrides are dissociated into their elements practically quantitatively at 500° C. The precise direct quantitative analysis of decaborane, as described by Stock (7) is somewhat difficult. However decomposition to boric acid and titration with barium hydroxide solution in the presence of mannite (7) is stated to be reliable even for very small amounts of boron.

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## FLUORINE

### Characteristics

Fluorine is the most reactive chemical element and this reactivity is shown by the fact that it combines with virtually every material (except the inert gases) under suitable conditions and with most materials spontaneously at room temperature. Fluorine, F, the first member of the halogen family of elements, is a colorless gas in dilute concentrations, but has a definite greenish cast in more concentrated quantities. It has a melting point of  $-223^{\circ}$  C., a boiling point of  $-188.3^{\circ}$  C., a density of 1.31 in gaseous form (air = 1) with a density of 1.14 for liquid fluorine. It has a pronounced odor which can be detected in concentrations of only a few parts per million. It can be compared to a relatively strong ozone odor, with some evidence of a chlorine-like smell. Fluorine is not a scarce element on the earth's surface and is found as fluorite ( $CaF_2$ ), cryolite ( $Na_3AlF_6$ ), and in silicates, such as tourmaline, topaz, and apatite. The scientific and technological advancement in the generation and handling of fluorine has been spectacular. Fluorine is now produced by electrolysis of a fused salt bath, such as potassium fluoride and hydrogen fluoride, at 100° C. with carbon anodes. It is difficult to transport because of its low critical temperature and because of its corrosive properties. It is, however, compressed into nickel and steel cylinders at 400 pounds per square inch by the liquefaction-pressure distillation method. Nickel and Monel metal have excellent corrosion resistance to fluorine; aluminum and magnesium are also good, while iron and steel have less corrosion resistance, particularly at high temperatures—at 480° C. and above (1).

### Industrial Uses

The domestic consumption of fluorspar was 497,012 tons in 1951 compared with 426,121 tons in 1950. The predominant purchaser (57 per cent in 1951) is the steel industry, which also consumes substantial quantities of hydrofluoric acid and sodium fluoride in which fluorspar is the basic material. Large amounts of sodium fluoride are used in the manufacture of rim steel. The second largest use (29 per cent in 1951) is in the manufacture of hydrofluoric acid, while the glass industry, which employs fluorspar as an opacifier and as a flux, uses 9 per cent of the fluorspar and ranks third in importance. Two outstanding wartime developments in the use of fluorine compounds, which have important peacetime possibili-

ties, are the aerosol insecticide bomb with dichlorodifluoromethane as a propellant, and the utilization of the anhydrous hydrofluoric acid alkalization process in aviation-gasolene manufacture. In the presence of hydrofluoric acid and certain other agents, paraffins will add to olefins, bringing about certain molecular rearrangements and yielding highly branched products which have good anti-knock value. Other wartime developments of note are its utilization in the preparation of uranium hexafluoride, which in gaseous form has made possible the separation of uranium isotopes, and its use as sulfur hexafluoride, which has proved to be an excellent insulator for high voltages. Boron fluoride etherate,  $(C_2H_5)_2OBF_3$ , used principally as a catalyst for the polymerization of vinyl ethers of olefins and other organic substances, is an important new substance and is now commercially available in quantity. Polytetrafluoroethylene is the first of the polymeric fluorine carbon derivatives to reach development in the plastics industry. The polymer, which appears under the trade name of Teflon, is characterized by its chemical inertness, resistance to change at high temperatures, and its extremely low dielectric loss factor. Popular interest has centered in the fluoride content of drinking water because of its role in causing mottled teeth, and also because of its apparent prevention of dental caries (2).

### Toxicity

Injury due to fluorides has largely resulted from exposure to fluoride dust or fume, burns from hydrofluoric acid, or to the ingestion of soluble fluorides. Most of the cases of acute intoxication, which have often terminated fatally, have resulted from the latter, where such substances as sodium fluoride were ingested by mistake or with suicidal intent. Recent technological advances have permitted the commercial utilization of elemental fluorine, and the hygienic significance of this substance is therefore of present interest. While the physiological properties of elemental fluorine have not been very extensively investigated, exposure to significant amounts of fluorine is said to be accompanied by gastrointestinal symptoms

and irritation of mucous membranes, particularly of the eyes and throat, as well as by skin damage. These symptoms are secondary in importance to the lung damage, and survival of the patient would depend on adequate oxygenation of the blood.

Burns from fluorine may be chemical or thermal, that is, caused by the heat of reaction of fluorine with the skin. The chemical burns resemble those due to hydrofluoric acid. After several hours, if the exposure is small, the lesion becomes reddened, then swollen and pale, with a macerated appearance, and is accompanied by severe throbbing pain. Necrosis and ulceration will follow if treatment is not instituted immediately after exposure. According to the treatment recommended by Landau and Rosen (3), washing should be continued for at least 15 minutes following contact, and the tissue beneath and around the affected area should be infiltrated with 10 per cent calcium gluconate, which precipitates the fluorine as inert calcium fluoride.

The soluble fluorides act as protoplasmic poisons (4). The soluble neutral salts destroy the cells of mucous membranes, while the acid causes deep tissue destruction and slow healing burns, which probably result from its specific toxic action. Exposure by inhalation to concentrations of hydrogen fluoride above 1.5 milligrams per liter for any period of time is dangerous for rabbits and guinea pigs, while concentrations below 0.1 milligram per liter have been tolerated for 5 hours without injury sufficiently severe to cause death (5). According to Greenwood (4), pathological changes which have been reported in organs and tissues as characteristic of fluoride intoxication should be accepted cautiously. In general, there appears to be some variation in the toxicity of different fluorine compounds and in the sensitivity of various species to the same fluorine compound. Extensive studies of the injurious effects of ingested fluorides have been made by McClure (6), while the effects of industrial exposure to fluorine have been reported by Roholm (7), by Machle (8), and by Truhaut (9).

Exposure to fluoride fumes in toxic concentrations usually manifests itself by a



sudden onset of chills, followed by a symptomatic period lasting one to two days or longer. A second phase follows, characterized by shortness of breath, a cough with scanty secretion, dyspnea, and elevated temperature. Cyanosis becomes apparent. The blood shows a leukocytosis and the sedimentation rate is increased. All these symptoms subside gradually. The duration of the process varies from 10 days to 2 months. Clinically, the pulmonary process is similar to bronchiolitis. While the comprehensive report of Roholm on the effects of exposure of workers to cryolite dust has pointed out the severe bone changes resulting from this exposure, no similar study has been reported involving osteosclerosis resulting from exposure to hydrofluoric acid. Lyth (10) reports a high incidence of dental mottling and spondylitis in two villages in China where the spring water contained from 2.4 to 13.1 parts per million of fluoride. Kilborn *et al.* (11) also discovered an endemic center of fluoride poisoning in Southwestern China in which case the toxicity of the drinking water produced a disabling arthritis and spondylitis. However Miller (12) states that the ingestion of 10 milligrams of nonacid fluorides per day is harmless to man, and Black and his associates (13) administered as much as 320 milligrams of sodium fluoride per day to human subjects for 5 or 6 months without evidence of acute or chronic toxicity. According to Hodges and his associates (14) the use of drinking water containing up to 3 parts per million of sodium fluoride apparently does not cause radiologically demonstrable sclerosis of the skeleton, even though the water is taken for a long period of time. Truhaut (15) has pointed out the difference between industrial and spontaneous fluorosis. The latter occurs where the soil or the drinking water is rich in fluorine. For instance a peculiar disease of domestic animals and man called "darmous" has been observed in French Morocco as well as in other parts of North Africa and is characterized by a complex dystrophy of the secondary dentition. This has been attributed to the use of water rich in calcium fluoride. McClure's recent experiments (16) indicate that

sodium fluorosilicate has apparently the same effects on teeth as sodium fluoride.

The popular interest in fluoride therapy in the prevention of tooth decay is increasing and many localities have requested the fluoridization of the drinking water supply. Badger (17) states that the level of fluoride should be maintained at no more than 0.7 parts per million in the drinking water to prevent defects in the permanent teeth of children. No experimental work has been reported at these low concentrations regarding the well-known powerful inhibitory effects of fluorides on enzyme reaction, specifically glycolysis, and the possible effects of this inhibition on human metabolism. Truhaut (15) has stated that the margin between beneficent effect and the toxic action of fluorides is extremely slight.

### Analysis

The microdetermination of fluorine presents certain difficulties which have made the method of estimation somewhat complicated. In order to isolate the fluorine prior to its determination, Willard and Winter (18) devised a method of distillation by means of sulfuric or perchloric acid. The distillate containing hydrofluoric acid is titrated with thorium nitrate, using sodium alizarin sulfonate lake as an indicator. Armstrong (19) improved this method by using alizarin sulfonate only as the indicator. Phosphates were found to interfere in the distillation by Churchill and his associates (20), necessitating a double distillation procedure. Talvitie (21) has adapted the thorium-alizarin lake method to the determination of fluorides in water low in interfering ions without prior distillation. Results may be obtained to 0.1 part per million of fluoride with 100-milliliter samples. When phosphates or aluminum are present, a preliminary distillation is required. The determination of fluoride in urine may be carried out by the distillation procedure indicated above (20).

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## GALLIUM

### Characteristics

Gallium, Ga, a member of the third group in the periodic table, is a hard, brittle, gray metal with a greenish-blue tinge. It has the remarkable property of melting at a point slightly above room temperature (29.75° C.). The molten metal is silver white in color. Gallium has an atomic weight of 69.72 and a density of 5.91. It boils at 1700° C. The liquid metal supercools readily and may be kept in the liquid state even at 0° C. Gallium like water expands on freezing. The vapor pressure of gallium even at high temperature is relatively low, thus even at 1031° C., the vapor pressure of gallium is only 0.004 millimeters of mercury and at 1116° C., the vapor pressure is but 0.023 (1). The gallic ion is colorless and its salts with colorless negative ions are white. The sulfates, nitrates, and halides are soluble but the solutions are highly hydrolyzed, especially with the latter group and precipitate basic salts on dilution or on boiling. Gallium forms a series of borohydrides, typified by dimethyl gallium borohydride, which have interesting physical properties (2).

### Industrial Uses

Gallium is used in high temperature measurement, for unlike mercury, gallium is non-volatile and resists oxidation at high temperatures (3). The gallium thermometer consists of a quartz capillary inside a quartz envelope. The capillary contains pure gallium with a slight trace of iron. Direct temperature readings up to 1200° C. may be made with this instrument. Gallium is used to some extent as a constituent of alloys in dental fillings.



## Toxicity

Gallium as the oxide, tartrate, benzoate, or anthranilate was used by Levaditi and his associates in the treatment of experimental syphilis and trypanosomiasis. Up to 15 milligrams per kilogram injected intravenously were tolerated without harm to laboratory animals (4). Meek, Harrold, and McCord (5) found that metallic gallium and gallium nitrate produced no skin injury and that intravenous and subcutaneous injection of relatively large amounts could be tolerated both by rabbits and rats without evidence of injury. Schwartz and Sieke (6) investigated the effect of gallium ammonium sulfate on animals and found a marked increase in polychromatic erythrocytes but no other changes after repeated subcutaneous injection of this salt in rabbits. Levaditi and his associates (7) demonstrated the fact that gallium remains in the tissues for long periods of time following intramuscular injection of soluble gallium salts. Tissue distribution experiments indicated that gallium behaves like bismuth, tellurium, and mercury with reference to its distribution in the tissues following injection. Dudley and his associates (8 to 12) have investigated the toxicology of gallium in connection with a study of the therapeutic application of radiogallium. Gallium lactate, which has an LD<sub>50</sub> value of 46 milligrams of gallium per kilogram for rats and 43 milligrams of gallium per kilogram for rabbits when injected intraperitoneally, apparently acts as a neuromuscular poison. It was found that gallium is deposited in the bones and that the gallium deposited in bone tissue is slowly released over a period of months. Further studies were made in regard to the possible therapeutic use of radiogallium Ga<sup>72</sup> in the treatment of osteogenic neoplasms.

## Analysis

The gallic ion resembles aluminum in many respects and, like aluminum, is completely hydrolyzed in the presence of the carbonate ion leading to the precipitation of the hydroxide. Gallium hydroxide, however, is appreciably soluble in ammonium hydroxide and an excess of this reagent must be

avoided. Quinalizarin forms a reddish lake with gallium hydroxide and this reagent is used for the colorimetric determination of gallium (13, 14). Sandell (15) has recently proposed a fluorescence method in which 8-hydroxyquinoline is used as reagent for the determination of gallium. As little as 0.1 microgram of gallium may be detected by this means. Dudley's recent photofluorometric method for gallium permits the determination of from 2 to 100 micrograms of gallium in biological materials (16). The sensitive arc lines for the spectrographic identification of gallium are 4172.05, 4033.01, 2943.64, and 2874.24.

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## GERMANIUM

### Characteristics

Germanium, Ge, atomic weight 72.60, is a grayish-white, brittle, lustrous metal with a density of 5.36, a melting point of  $958^{\circ}\text{C}.$ , and a boiling point of  $2700^{\circ}\text{C}.$  Germanium dissolves in aqua regia but not in hydrochloric acid. Nitric acid oxidizes the element to white germanic oxide ( $\text{GeO}_2$ ). It is oxidized at high temperature and combines directly with the halogens. Germanium is found in several sulfide ores, especially those of silver, lead, tin, antimony, and zinc. Among the many rare elements found in coal ash, germanium and gallium appear to be the only ones that it may be feasible to recover commercially. The two oxides of germanium,  $\text{GeO}$  and  $\text{GeO}_2$ , are slightly soluble in water, forming faintly acid solutions; they also dissolve in acids but form no oxy-salts (1). Germanium forms a hydride having the formula  $\text{GeH}_4$ , which is a gas liquefying only at low temperatures and which is moderately stable at room temperature.

### Industrial Uses

Recent interest in germanium has encouraged commercial production of the pure metal and its oxide as by-products in the recovery of cadmium from zinc sintering-plant dust. Although similar to silicon in many properties, there are sufficient differences to encourage the use of the much more costly germanium in some electrical, metallurgical, and ceramic applications (2). The property of slight expansion on solidification aids in making castings of good dimensional tolerance. Germanium possesses the property of semi-unidirectional transmission of electricity and is finding use as a rectifier for ultra-high frequencies (3) and in making high-resistance resistors. The development and improvement of germanium diodes and transistors has been revolutionary in the field of electronics and this probably constitutes the most important use for germanium at the present time. It is used as an

alloying agent with aluminum, magnesium, gold, and platinum; as a substitute for silicon in various alloys; and in optical glass to give higher refractive power. Relatively large quantities of gallium, germanium, and indium could be saved as by-products of the zinc industry. Studies of ashes and gas works dust from British coal show that significant amounts are being dissipated in the atmosphere or discarded as useless dust annually from this source (4).

### Toxicity

Because of its close chemical relationship to arsenic, germanium has been investigated with reference to experimental and human anemias. Hammett and associates (5) found that germanium dioxide stimulated the generation of red blood cells and showed no significant toxic properties. Muller (6) tested the toxicity of two allotropic forms of the oxide. The minimum lethal dose as determined by intraperitoneal injection for the ordinary crystalline oxide is about 300 milligrams per kilogram body weight in guinea pigs and that for vitreous colloidal germanic oxide is 400 milligrams. The quantities administered indicate that both forms are relatively nontoxic and that germanic oxide is 22 times less toxic than arsenic trioxide. Either form given in sublethal amounts brings about a pronounced tolerance. Observations on the excretory rate of germanic oxide were made by Muller in man after the oral introduction of 356 milligrams of germanic oxide. A total of 276.4 milligrams was demonstrated within 7 days in the feces (60.60 milligrams) and urine (215.8 milligrams), showing that the kidney is the main excretory organ for this compound. Hueper (7) considered the fluctuations in the number of erythrocytes to be evidence of changes in water content of the blood and not due to a stimulative effect of germanium on the bone marrow. He believed that the loss of weight in rabbits treated with toxic doses of germanium dioxide was due to dehydration and was caused only to a lesser extent by an increase in oxidative processes of the organism. Toxic doses caused a marked drop in blood pressure and in the production of massive brown precipitations



in various organs. Hueper reviewed the physiologic and pharmacologic effects, as well as the toxic action of germanium and its compounds. He concluded that germanium compounds exhibit a much lower toxicity than the corresponding lead and tin compounds. Harrold and associates (8) found that germanium dioxide unlike silicon dioxide does not produce proliferative responses upon intraperitoneal injection into guinea pigs, that buffered germanium dioxide solution is not a primary skin irritant, and that blood counts taken on rats and guinea pigs after the injection of germanium dioxide showed no significant changes. Germanium hydride,  $\text{GeH}_4$ , is an hemolytic gas which has been shown to cause toxic manifestations in concentrations of 100 parts per million and death in concentrations of 150 parts per million (9).

Recent investigations at the U. S. Naval Medical Research Institute have added much to our knowledge of the physiological importance of germanium (10, 11, 12). Dudley (13) has shown that neither parenteral injection of suspensions of germanium or germanium oxide nor inhalation of the dust of these substances constitutes a serious health hazard. The rate of clearance of germanium and germanium oxide dusts from the lungs of rats indicates that these materials are rapidly eliminated through oxidation or simple solution. No deaths occurred during the exposure period and no irritation nor gross pathological changes were observable in the animals at autopsy. It would therefore appear that germanium does not constitute an acute industrial hazard.

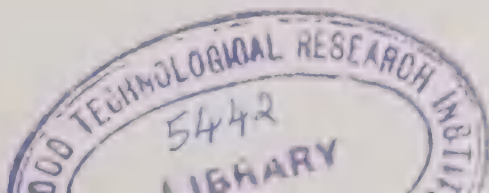
### Analysis

There are no specific color tests for the detection and determination of germanium, although in common with a number of other substances, germanium salts react with such substances as quinalizarin (14) and *p*-nitrobenzene-azo-chromotropic acid, the former being the more sensitive. White germanic sulfide,  $\text{GeS}_2$ , is precipitated by hydrogen sulfide from strongly acid solutions of germanium salts. The precipitate is soluble in ammonium sulfide. The reactions for germanium compounds resemble somewhat

those of tin and silicon. Hueper (7) gives in detail the method developed by Buchanan and used by Muller for the determination of germanium in urine, feces, and tissues. The method depends on the volatility of germanium tetrachloride from an aqueous hydrochloric acid solution in a current of chlorine. By this method germanic oxide can be detected in as small a quantity as 0.0002 gram. According to Alimarin and Ivanov-Emin (15), polarography permits germanium determinations in acid solution in dilutions as great as 1 part per million. However, arsenic, lead, and tin interfere with this determination. Sensitive spectral lines for the detection of germanium are 4685.84, 3039.08, and 2651.61.

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## GLASS FIBER AND MINERAL WOOL

Under the general heading of glass wool there are various trade products, of which Fiberglas and rock wool or mineral wool are outstanding. Rock or mineral wool is a substance composed of very fine interlaced mineral fibers, having the appearance of loose wool or cotton, and made by directing jets of steam into a stream of molten slag, which is shredded into wool. Rock and slag wools differ widely in composition, but a typical wool is composed of about 42 per cent  $\text{SiO}_2$ , 12 per cent  $\text{Al}_2\text{O}_3$ , 34 per cent  $\text{CaO}$ , 10 per cent  $\text{MgO}$ , and 1 per cent  $\text{Fe}_2\text{O}_3$ . With too great a calcium content the wool tends to disintegrate, and sulfides also cause deterioration. The raw materials may differ greatly in character and may consist of argillaceous limestone, shales or lead, iron or copper slags. Various substances, such as limestone, dolomite, or quartz, are added in order to make a more easily melted and fluid mix.

Fibrous glass is a glass product made by a mechanical process which results in a flexible fiber form. Various processes have been evolved to accomplish this—such as by directing a stream of fluid glass upon a rapidly revolving refractory disc or by causing the stream of glass to flow vertically through fine platinum nozzles and to feed in compressed air concentrically around this stream. The tensile strength of glass fibers increases rapidly as the diameter decreases, especially below two thousandths of an inch. With fibers two ten-thousandths of an inch in diameter, the length has been calculated as 4,356 miles per pound. Glasses have been developed which are resistant even under extreme conditions. These glasses are usually low in alkali. In the manufacture of staple fibers, molten glass falling from a multitude of fine holes is met by jets of high pressure steam which yields a large number of fibers, which are so small as to be nearly invisible and which are essentially endless. From this, yarn is made, which is used much the same as any other textile material. Such

fibers are woven into textiles, such as curtains and hangings, separators in storage batteries, and filter media in filter presses, and are also used as a reinforcement for plastics and as a filling for nonallergenic pillows and mattresses. For medical purposes it is used as a blood plasma filter, surgical suture material, a tracer thread which is opaque to X-rays in surgical sponges, and for light-weight artificial limbs. Rock or mineral wool is largely used as insulating material in houses.

## Hygienic Significance

There are two aspects of the question of possible health hazard associated with mineral wools or fibers. The first is related to possible pulmonary injury due to inhalation of very fine fragments, and the second to skin irritation. Fairhall and his associates (1) investigated the effect of this material on animal life. In this study, cats were exposed to oil-extracted and finely ground rock wool dust, as well as to hot and cold air blown through commercial rock wool. The average particle size of the floating dust was 2.2 microns. No significant pathological changes were found in the tissues of any of the animals so exposed. The lungs of the cats heavily dusted with ground mineral wool contained large numbers of refractile silicate particles. Apart from the presence of silicate particles, however, no abnormalities were noted. The absence of wide-spread inflammatory changes in the lungs, where silicate particles were in intimate contact with the tissues, indicated the absence of irritation and the accompanying changes in the lungs were those which one might expect any inert foreign matter to produce. The essentially negative chest findings among workers reported by Carpenter and Spolyar (2) in the mineral wool industry, Gardner's report (3) of the lack of pulmonary damage from exposure to glass wool, the absence of lung pathology noted by Desoille and Dhers (4), and the report of Champeix (5) with reference to glass fiber, indicate that work with these substances does not represent a major danger to the worker's health.

The temporary skin irritation noted among workers handling fiber glass products



or certain mineral wool has been a source of complaint. This dermatitis, according to Schwartz and Botvinick (6), is caused by the mechanical impingement of tiny glass slugs on the skin in handling the material and occasionally is due to sensitivity to the tricresyl phosphate, which is added to the glass wool as a dust adhesive or to tar or the phenol-formaldehyde resin binder. Leder (7) has made histologic examination of the minute lesions resulting from the handling of glass wool and finds that these are never of an allergic eczematous character. Infectious folliculitis may occur, but never an eczema. Erwin (8) reports that with the continued use of Fiberglas, most of the workers become "hardened" and the temporary itching, swelling, and redness subside. Reassurance and treatment with calamine lotion and phenol, plus the other protective measures instituted, handled 95 per cent of the cases of temporary skin irritation.

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### HYDRAZINE

#### Characteristics

Anhydrous hydrazine,  $\text{NH}_2\text{-NH}_2$ , is a colorless liquid having a boiling point of  $113.5^\circ\text{C}$ . and a solidifying point of about  $0^\circ\text{C}$ . The colorless crystals melt at  $1.4^\circ\text{C}$ . The liquid is somewhat heavier than water

and has a specific gravity of 1.011 at  $15^\circ\text{C}$ . It is very soluble in water, in which it dissolves with rise of temperature. Commercially hydrazine is prepared by the oxidation of ammonia with sodium hypochlorite in aqueous solution made viscous with 0.2 per cent of glue. Anhydrous hydrazine is prepared from the hydrate by the action of metallic calcium, or by repeated distillation from barium oxide. Hydrazine hydrate,  $\text{NH}_2\text{-NH}_3\text{OH}$ , may be obtained by the fractional distillation of the aqueous solution and is a colorless, fuming liquid having strongly basic properties. It corrodes glass like caustic alkalies and destroys cork and india rubber. Hydrazine is a powerful reducing agent, readily reducing copper and silver salts to the respective metals.

#### Uses

Hydrazine is of particular interest at the present time because of its application as fuel for jet motors and rockets (1). It readily reacts with hydrogen peroxide, but, as ignition of the mixture is somewhat delayed, a catalyst is added. Typical rocket fuel is a mixture of hydrazine hydrate, methyl alcohol, and a copper catalyst,  $\text{K}_3\text{Cu}(\text{CN})_4$  (2).

#### Toxicity

Hydrazine salts are very poisonous to lower forms of life and they also affect enzyme activity to some extent, although the sulfate has but little action on peroxidases. With large doses of hydrazine dogs pass into a coma with a decrease in body temperature of about 10 degrees. The blood of hydrazine-poisoned dogs is apparently not spectroscopically changed. Allantoin excretion is increased but this increase apparently results from increased endogenous metabolism. The lethal dose for dogs and rabbits is about 1/10 of a gram per kilogram of body weight. The daily injection of 35 milligrams of hydrazine sulfate in rabbits for 1 week does not produce symptoms of intoxication (3). However, Pennetti and DeRitis (4) have found that this salt, when added to a normal diet for rabbits, produces a diminution of ascorbic acid in the liver. Krop (5) in a review of the toxicology of hydrazine

states that the lethal inhalation level varies from 100 to 576 milligrams per cubic meter for rats and that the LD<sub>50</sub> value for hydrazine administered intraperitoneally in mice is 163 milligrams per kilogram. Witkin (6) found the LD<sub>50</sub> value for hydrazine administered intravenously in dogs to be 25 milligrams per kilogram; in mice 57 milligrams per kilogram; in rats 55 milligrams per kilogram. The oral and intraperitoneal values for rats and mice were only slightly in excess of these values. Cole and his associates (7) have found that hydrazine poisoning in mice may be successfully treated by the combined parental administration of thiopental-sodium and sodium pyruvate.

### Analysis

Singh and Ilahi (8) have evolved a potentiometric method which they state may be satisfactorily used for the determination of hydrazine. Pesez and Petit (9) have found *p*-dimethylaminobenzaldehyde in dilute sulfuric acid a suitable means of determining hydrazine colorimetrically. In atmospheric samples containing both ammonia and hydrazine vapor, McKennis and Witkin (10) have evolved a colorimetric procedure for determining both these substances.

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## HYDRAZOIC ACID

### Characteristics

Hydrazoic acid, hydrogen azide, azoimide, HN<sub>3</sub>, is a colorless, water-white mobile liquid boiling at 37° C. It crystallizes at a low temperature and melts at -80° C. It is a monobasic acid miscible with both alcohol and water. The anhydrous acid is distinctly volatile at room temperature and solutions containing less than 30 per cent of the acid give off its vapor. Ammonia gas in contact with this vapor forms dense fumes of ammonium azide. The acid readily forms salts with many metals and these azides may readily be prepared in the pure, crystalline state. In these salts, the acid is always monobasic and the formulae correspond to those of the halides. The acid attacks many metals with the evolution of hydrogen. In some cases, as with zinc and aluminum, both hydrogen and ammonia are evolved. Hydrazoic acid and especially its metallic derivatives are explosive. Hydrazoic acid may be prepared from hydrazine hydrate and potassium nitrate, followed by distillation. More generally, however, it is prepared by the interaction of sodamide and nitrous oxide, followed by distillation from either sulfuric or phosphoric acids ( $\text{NaNH}_2 + \text{N}_2\text{O} = \text{NaN}_3 + \text{H}_2\text{O}$ ). It may be conveniently prepared in small amounts by acidifying sodium azide, extraction with ether, and evaporation of the ethereal extract. A method has been recently developed for the direct synthesis of hydrazoic acid from nitrogen and hydrogen by streaming these gases through a glow discharge at low temperatures (1). Hydrazoic acid has a sickly, penetrating, and most unpleasant odor.

### Industrial Uses

Hydrazoic acid has no practical importance in industry except as a source of certain metallic azides. While the salts of the metals of the alkalis and alkaline earths are not nearly so explosive as those of the heavy metals, the latter, particularly lead azide, are used for war purposes as shell detonators. Lead azide, Pb(N<sub>3</sub>)<sub>2</sub>, is a more efficient detonating agent than mercury fulminate (2) and has other advantages in that it requires a higher temperature for its spontaneous ex-



plosion and does not decompose on long-continued storage. No data are at present available concerning the production and consumption of lead azide during World War II.

### Toxicity

Hydrazoic acid vapor produces unpleasant after-effects when inhaled. The most marked effect noticeable is the eye irritation and headache following inhalation in low concentration; in greater concentrations, it causes death. Fairhall and his associates (3) found that up to about 900 parts per million of azoimide is not lethal when breathed by rats and guinea pigs for 1 hour. At a concentration beyond this point, however, its lethal effect is notable and beyond 1,160 parts per million its lethal action is invariable when it is breathed for one hour. It is invariably fatal in exposures of one-half to three quarters of an hour to concentrations of about 1,300 parts per million. Very high concentrations of 2,900 parts per million invariably cause death when inhaled for as short a period as 10 minutes. A degree of excitability is apparent at the initial stage of exposure. This is followed by dyspnea with flank breathing, lacrymation, salivation, and loss of muscular coordination of the extremities. These phenomena are followed by clonic convulsion, then toxic convulsion, and death. Since hydrazoic acid gas proved invariably fatal in concentrations beyond 1,160 parts per million, this substance should be classed as a dangerous gas. Graham and his associates (4) made a clinical investigation of employees in a lead azide factory and failed to find any evidence of pathological change attributable to exposure to hydrazoic acid vapor. In animal experiments, these investigators found that hydrazoic acid given by injection in small doses produced a rapid, profound, and long-maintained fall in carotid blood pressure and a transient stimulation of respiration. In high dosage, hydrazoic acid was extremely toxic.

### Analysis

In the absence of other acid or alkaline vapors, hydrazoic acid vapor may be trapped in a known amount of standard alkali by bubbling a measured volume of air

through a fritted gas bubbler and back-titrating. Hydrazoic acid may be quantitatively determined by oxidation with iodine. When a slight excess of iodine is added to a neutral or alkaline solution, nitrogen is evolved and may be volumetrically measured. In very dilute solutions, ceric nitrate or sulfate should be added to promote the evolution of nitrogen. The reaction between an azide and nitrous acid is similarly quantitative. Neutral alkali salts of hydrazoic acid give a blood-red coloration with ferric salts similar to that produced by thiocyanates and may be usefully employed for the colorimetric determination of azoimide.

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## HYDROCHLORIC ACID

### Characteristics

Hydrochloric acid, known in its crude form as muriatic acid, is a solution of hydrogen chloride in water. Pure hydrogen chloride is either a colorless gas or, when liquefied, a colorless, fuming, pungent liquid. At 0° C., 1 liter of gas weighs 1.6392 grams and the specific gravity is 1.268 (air = 1). Liquid anhydrous hydrogen chloride boils at -85° C., melts at -111.5° C., and has a specific gravity of 1.194 at -85.8° C. The solubility in water is 82.3 grams per 100 milliliters at 0° C.

Hydrochloric acid is commonly made by the action of sulfuric acid on sodium chloride as a by-product in the manufacture of soda ash. It is also made from the by-product recovery of hydrogen chloride in the chlorination of organic compounds and by the burning of hydrogen in chlorine. Of the 56 plants making hydrochloric acid in 1943, 30 per cent were situated on or near New York harbor, with 11 plants in New Jersey.

### Industrial Uses

Industrially, hydrochloric acid is used extensively in various chemical processes, such as the pickling of metals, particularly steel (for scale removal), in the production of glucose and corn sugar from starch, and in the refining of cane sugar. It is employed in the manufacture of synthetic rubbers, plastics, tetraethyl lead, glue, chemicals, and, in smaller quantities, in the processing of textiles, rayon, leather, dyes, fatty acids, oils, reclaimed rubber, and pigments. It reacts with organic acid anhydrides to form acid chlorides, and the anhydrous gas is used to form alkyl chlorides through reaction with alcohols, ethers, and unsaturated hydrocarbons. In 1953, the United States produced 773,500 short tons of 100 per cent hydrochloric acid.

### Toxicity

Hydrogen chloride when exposed to air forms dense white fumes from the condensation of atmospheric moisture and the formation of hydrochloric acid in solution droplets. The gas is seldom encountered in the anhydrous state and irritations is caused by skin contact with these droplets. The toxicity of hydrochloric acid as droplets is less than that of anhydrous hydrogen chloride. Machle and his associates (1), in a study of the effect on animals of inhalation of hydrogen chloride, demonstrated that hydrogen chloride has nearly the same immediate toxic action as hydrogen fluoride, but produces less serious residual effects. Exposure to hydrogen chloride in a concentration of 1 milligram per liter for 6 hours killed all animals. Animals exposed to 0.05 milligram per liter, for 6 hours a day, 5 days a week for 4 weeks showed no immediate toxic effects and no pathological changes.

Upon investigating the increased illness among workmen engaged in chemical works where hydrochloric acid and sodium sulfate are produced, Bransburg and Karacharov (2) found the complaints were chiefly disorders of the gastrointestinal tract. About 20 per cent of the workmen suffered from gastritis with abnormal acidity of the gastric juice. Many cases of chronic bronchitis were observed, while among other workers an

acute process of dental destruction was observed. Chemical analysis of the air in this case showed that during many phases in the production the fumes of hydrochloric acid escaped into the air. Hydrochloric acid has had some therapeutic applications in dilute form, although, in general, evidence of benefit from injection of extremely dilute solutions is lacking (3). Henderson and Haggard (4) state that 35 parts per million causes irritation on short exposures, and that 50 to 100 parts is the maximum concentration tolerable for 1 hour.

### Analysis

Various methods have been proposed for the determination of hydrogen chloride acid vapor as an aerial contaminant. In the absence of other acid vapors or gases, hydrochloric acid may be absorbed and titrated. In the absence of other chlorides it may be determined nephelometrically as silver chloride. Fairhall and Heim (5) have developed a rapid procedure for the micro determination of chlorides. By means of this method, a fraction of a milligram of chloride in 0.1 milliliter of solution may be determined with an accuracy of about 2 per cent.

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## HYDROGEN FLUORIDE

### Characteristics

Hydrogen fluoride, hydrofluoric acid, (HF), a mobile, fuming liquid, solidifying at  $-82.9^{\circ}\text{C}$ ., and boiling at  $19.5^{\circ}\text{C}$ ., results from the action of fluorine on water. Commercially it is prepared by heating fluorides with sulfuric acid and trapping the evolved hydrofluoric acid in water. It has a



specific gravity of 0.9879 at 12.5° C. The commercial acid is a solution of hydrofluoric acid in water. The most characteristic property of hydrofluoric acid is its ability to dissolve glass and, because of this, it must be kept in platinum, wax, or hard rubber and must be prepared in platinum or lead vessels. Hydrofluoric acid gas is colorless, has a penetrating odor, and its density is 0.713 (air = 1). The constant-boiling mixture of the system HF-H<sub>2</sub>O was found by Munter and his associates to have a composition of 38.26 per cent hydrofluoric acid and a boiling point of 112.0° C. at 750.2 millimeters of pressure (1). The vapor pressures of hydrofluoric acid solutions (2 to 30 per cent hydrogen fluoride) at 25°, 40°, 60°, and 75° C. were determined by Brosheer and his associates (2).

### Industrial Uses

The industrial consumption of hydrofluoric acid which amounted to only 14,842,000 pounds in 1939, increased to a maximum of 246,250,000 pounds in 1951. Anhydrous hydrogen fluoride is used extensively by the petroleum industry in the synthesis of high octane gasoline by alkylation, and in the manufacture of aluminum fluoride which is of importance in the commercial production of metallic aluminum. Artificial cryolite, refrigerants, insecticides, the electrolytic refining of metals, the pickling of metals, electroplating operations, and the etching of glassware, all use considerable quantities of hydrogen fluoride.

### Toxicity (See section on Fluorine)

Hydrofluoric acid, in addition to causing deep burns on skin contact, also acts as a protoplasmic poison. The fumes or mist of this acid on inhalation have been found to act as primary irritants, and continuous exposure to an atmosphere contaminated with even low concentrations causes severe inflammation of the respiratory tract. This may result in a pneumonitis. Exposure by inhalation to concentrations of hydrogen fluoride above 1.5 milligrams per liter for any period of time is dangerous for rabbits and guinea pigs while concentrations below 0.1 milligram per liter have been tolerated

for 5 hours without injury sufficiently severe to cause death (3). Apart from the irritation arising from its corrosive and acid properties both hydrofluoric acid and its neutralization products such as sodium fluoride are direct cellular poisons and inhalation may cause deep ulcers in the upper respiratory tract. Hydrofluoric acid is intensely caustic to mucous and skin surfaces and burns or ulcers caused by this substance heal very slowly. After contact with hydrogen fluoride, there is a latent period varying with the degree of exposure. Treatment after immediately flushing the skin with a large amount of water for 15 minutes consists in injecting the tissue beneath and around the affected area with 10 per cent calcium gluconate (4, 5, 6). A note in the Journal of the American Medical Association (7) states that the use of triple dyes in the treatment of hydrofluoric acid burns has been discarded by one consultant and that the calcium gluconate treatment has also been abandoned because the injections contributed to sloughing. According to Henderson and Haggard (8), a concentration of from 50 to 250 parts per million is dangerous for even short exposures.

### Analysis

Where hydrofluoric acid is the sole atmospheric contaminant various methods of titration will recommend themselves to the analytical chemist. Usually, however, the fluoride content of the air, in addition to the acid content, will be of importance and various colorimetric procedures such as the zirconium nitrate-sodium alizarinate method or its cerous nitrate modification may be used (9). Lamar's use of this method for the determination of fluoride in water (10) has been modified by Setterlind to conform to the requirement and procedures necessary in air analysis (11).

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## HYDROGEN PEROXIDE

### Characteristics

Hydrogen peroxide, hydrogen dioxide,  $H_2O_2$ , is a colorless, somewhat unstable liquid having a density of  $D_{20/4}$  1.438, boiling point of  $151.4^\circ C.$  at 760 millimeters and a freezing point of  $-0.89^\circ C.$  It is miscible with water in all proportions, soluble in ether and insoluble in petroleum ether. It is prepared by the anodic oxidation of sulfuric acid at a low temperature, which results in persulfuric acid,  $H_2S_2O_8$ , and which in turn yields hydrogen peroxide on hydrolysis. The latter is then distilled off under reduced pressure. A continuous process has also been developed in which hydrogen peroxide is made from ammonium persulfate. The older process of treating barium dioxide with sulfuric acid is still used to some extent, since the resulting barium sulfate is a salable by-product known as *blanc fixe* and used in paper manufacture. An aqueous solution of hydrogen peroxide may be concentrated to 30 per cent by distillation at atmospheric pressure and to anhydrous  $H_2O_2$  with high-vacuum distillation. Solutions of hydrogen peroxide are usually stabilized with acetanilide, because the rough surface of the container, even of glass, is sufficient to cause decomposition of the pure substance. At atmospheric pressure, vapor containing 26.0 mol per cent of hydrogen peroxide can be exploded by a hot wire or spark gap (1).

### Uses

Hydrogen peroxide in its dilute form is widely used in industry as a bleaching agent, as an oxidant, in pharmaceutical preparations, and to some extent as an antiseptic. The export of hydrogen peroxide from the United States in 1953 amounted to 1,321,265 pounds.

### Toxicity

Hydrogen peroxide is not toxic in the usual sense. It is dangerous because of its strong caustic nature. Thirty per cent hydrogen peroxide is especially caustic and can cause serious burns. Even 3 per cent peroxide used as a mouthwash can cause hypertrophied papillae of the tongue with continued use. Krachkow (2) has pointed out the hazard of skin contact with concentrated hydrogen peroxide and refers especially to corneal damage from splashes which can lead to permanent blindness. Barsotti and his associates (3, 4) have reported eczema and asthma among workers in a factory producing hydrogen peroxide from ammonium persulfate and potassium persulfate. In this plant the atmospheric concentration of peroxides amounted to 0.2 milligrams per cubic meter. Oberst and his associates (5) found that the vapor of 90 per cent hydrogen peroxide in a concentration of 7 parts per million produces lung irritation in laboratory animals. They estimate that exposure of men to less than 4 parts per million daily for long periods of time would not produce serious results. In view of its thermal instability, i.e., tendency to self-heat, Shanley (6) has pointed out the necessity for special care in the design of storage areas for hydrogen peroxide.

### Analysis

A number of methods depending upon its oxidizing nature have been proposed for the determination of hydrogen peroxide. One of the sensitive methods for minute amounts is the ammonium molybdate procedure of Isaacs (7) in which a yellow color is produced in citric acid solution and comparison made with potassium chromate standards.



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## HYDROGEN SULFIDE

## Characteristics

Hydrogen sulfide, hydrogen monosulfide,  $\text{H}_2\text{S}$ , is a gas at ordinary temperatures. It melts at  $-85.4^\circ \text{C}$ . and boils at  $-60.3^\circ \text{C}$ . It is soluble in water to the extent of 290 volumes per 100 volumes of water at  $20^\circ \text{C}$ . and 1 atmosphere pressure, and the resulting concentration is about 0.1 M. Hydrogen sulfide is an extremely weak dibasic acid. It is somewhat heavier than air, for the specific gravity is 1.19 (air = 1). It tends, therefore, to accumulate in deep cavities, such as vats and cellars, under stagnant conditions. It has a powerful, characteristic odor usually identified with putrefaction.

## Industrial Importance

The importance of hydrogen sulfide in industrial hygiene lies in its nuisance value, rather than its usefulness. It is a side product of many reactions and processes, and because of its dangerous properties and/or disagreeable odor requires careful elimination or control. A considerable amount of hydrogen sulfide is removed from city gas by iron oxide purifiers or by scrubbing with alkali, or with sodium phenolate, triethanolamine, or sodium arsenite. The latter, known as the Thylox process, yields sulfur as an end

product, which in turn is used as a dusting agent in agriculture, or for the manufacture of sulfuric acid. Hydrogen sulfide is evolved as a waste product in a variety of chemical manufacturing operations and technical processes. In the viscose rayon industry, hydrogen sulfide is evolved in large amounts, necessitating careful enclosure of various operations. Hydrogen sulfide arises from the decomposition of sewage and is frequently a source of danger to workmen in sewerage installations. It is also a hazardous substance in oil fields in which gases with a high content of hydrogen sulfide gas are frequently encountered (1, 2)

## Toxicity

Hydrogen sulfide, even in comparatively low concentrations, is destructive to most forms of life. The gas is a primary irritant, but the systemic action caused by absorption of the products resulting from neutralization of the sulfide by the alkali of the moist tissues of the respiratory tract overshadows its irritant action. When exposed to low concentrations of the gas, local irritation of the eyes, nose, and throat ensues, and is indicated by pain and congestion of the conjunctiva, sneezing, dryness, and soreness of the mouth and throat, and increased secretion of tears, saliva, and mucus. Headache, giddiness, and loss of energy may appear only after some time. Death following exposure to the lower concentrations partly occurs from edema of the lungs resulting from its irritant effect. A concentration of 200 parts per million is sufficient to cause symptoms in man. Slight symptoms may appear after exposure to an atmosphere of 100 parts per million for several hours. Exposure to 1,000 parts per million is rapidly fatal. While hydrogen sulfide is commonly thought to cause asphyxia due to combination with hemoglobin and interference with the oxygen-carrying capacity of the blood, it does not in fact combine with oxyhemoglobin, but only with methemoglobin, which is not normally present in the blood. Systemic poisoning is caused by the action of the free hydrogen sulfide carried by the blood and its action on the nervous tissue

throughout the body. In particular, hydrogen sulfide causes paralysis of the respiratory tract and consequently, asphyxia. In lower concentrations, there is a stage of preliminary stimulation of the respiratory center; in high concentrations immediate paralysis occurs and death rapidly follows. Numerous cases with fatal outcome have been reported in the literature, the cases recently reported by Freireich (3) being typical. In addition to the hazard of hydrogen sulfide formed by the decomposition of waste material, stream pollution may be an occasional factor. Troisi (4) found that water taken from a stream containing the run-off from a rayon factory was sufficiently rich in hydrogen sulfide to cause symptoms of hydrogen sulfide poisoning among employees of a beet sugar plant located downstream. It is a nonaccumulative poison, and, if the victim is revived by artificial respiration, there are no systemic sequelae. The maximum allowable concentration of hydrogen sulfide has been set at 20 parts per million of air by volume (5).

### Analysis

Owing to its pronounced organoleptic properties, hydrogen sulfide may be detected by the sense of smell in extremely low concentrations. As the atmospheric concentration is increased, however, this response may become dulled to the point where dangerous concentrations may exist without detection. Hydrogen sulfide may be detected chemically by its tendency to darken lead acetate paper or silver nitrate paper, or by the formation of a blue color (methylene blue) with *p*-aminodimethylaniline in the presence of hydrochloric acid and ferric chloride (6). In alkaline solutions, soluble sulfides give an intense violet coloration with sodium nitroprusside. Quantitatively, hydrogen sulfide may be determined colorimetrically by its reaction with *p*-aminodimethylaniline (7). Convenient volumetric methods are based on oxidation with potassium permanganate or iodine (8). A recent spectrophotometric method for hydrogen sulfide in gases permits the determination of as little as 7 micrograms of hydrogen sulfide with a precision of 10 per cent (9).

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## HYDROXYLAMINE

### Characteristics

Hydroxylamine,  $\text{NH}_2\text{OH}$ , is a colorless, odorless crystalline solid melting at 33° C. and boiling at 58° C. (under pressure of 22 millimeters). Its density is 1.227. Hydroxylamine is very soluble in water and somewhat soluble in alcohol and in ether. It deliquesces and oxidizes on exposure to air, inflames in dry chlorine, and is readily decomposed to ammonia, nitrogen, and water. Its aqueous solution is strongly alkaline and with acids it forms well-defined, stable salts. It is a strong reducing agent, forming cuprous and mercurous compounds from the divalent salts and reducing silver salts to metallic silver. With aldehydes and ketones it forms oximes. Many substituted hydroxylamines are known. Hydroxylamine is prepared commercially as the sulfate by the interaction of sodium nitrite, acid sodium sulfite, and potassium chloride, which yields potassium hydroxylamine disulfonate  $\text{HO} \cdot \text{N}(\text{SO}_3\text{K})_2$  and which is then converted to hydroxylamine sulfate.

### Uses

The salts of hydroxylamine are used as reducing agents in analytical chemistry; in



synthetic organic chemistry for the preparation of oximes; as reducing agents in photography; and commercially in tanning, in the textile industry, and as antioxidants for fatty acids and soaps.

### Toxicity

While hydroxylamine is toxic to all living cells, it appears to have but little action on enzyme systems in general with the exception of its slight effect on catalase. Aqueous neutral solutions of the salts of hydroxylamine also have but little action on the skin or mucous membranes beyond a slight erythema and burning sensation. Hydroxylamine is not found in the urine following its administration to animals (rabbits). It produces a profound effect on the blood of warm- and cold-blooded animals, however, converting oxyhemoglobin to methemoglobin. Jacobsen and his associates (1) injected a group of 175 rabbits intravenously daily for long as 19 months. The changes produced were similar to those following treatment with other substances causing methemoglobinemia. Hurst (2) found that repeated administration of hydroxylamine to sheep in amounts compatible with survival caused demyelination of brain tissue within periods of 184 days. In thyroidectomized rabbits Wislicki and Gerendasi (3) have shown that, while hemoglobin and erythrocyte reduction were greater than in the control animals, the toxic effects of hydroxylamine were not marked until after the eighth day. Hydroxylamine does not inhibit the nicotin-catabolizing enzyme according to Von Werle and Müller (4), but has been found by Perlmann and Lipman (5) to have some effect on catalase.

There is very little literature in general concerning the oral administration of hydroxylamine, and most of the investigations reported have centered around the parenteral administration of this substance. Recently, however, Riemann made an experimental investigation of the effect of oral administration of hydroxylamine to rats and mice and found the lethal dose ( $LD_{50}$ ) for hydroxylamine in mice to be about 410 milligrams per kilogram of body weight (6). For comparison the  $LD_{50}$  dose of sodium

nitrite is 214 milligrams per kilogram of body weight. The feeding of 330 to 380 milligrams per kilogram of body weight of hydroxylamine daily for 178 days had no influence on the growth of rats. However the experimental animals were found to have spleen weights four or five times that of the control animals. At the same time a pronounced reduction in the weights of the thyroid gland was noted. No disturbance in the general condition of the experimental rats was observed at any time during the experiment. There is no record of industrial poisoning due to the manufacture or handling of hydroxylamine.

### Analysis

Numerous methods have been proposed for the analysis of hydroxylamine and have for the most part been based upon its powerful reducing action. Of these methods that of Raschig appears to be the best. In this method the proportion of ferric sulfate reduced in acid solution is found by titration of the ferrous iron with permanganate and the corresponding amount of hydroxylamine calculated.

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### INDIUM

#### Characteristics

Indium, In, atomic weight 114.76, is a silvery-white, soft metal unaffected by exposure to air, with a melting point of 155° C. and a boiling point somewhat above 1450° C. Its density is 7.3. Heated in air, it burns with a blue flame yielding indium

trioxide. The indic ion,  $\text{In}^{+++}$ , is colorless, ammonia or alkali hydroxide precipitating the hydroxide,  $\text{In}(\text{OH})_3$ . The nitrate, sulfate, the alums, and the halides are soluble, the latter resembling cadmium compounds in that they are weak salts. Yellow indium sulfide,  $\text{In}_2\text{S}_3$ , is precipitated by hydrogen sulfide in the presence of very dilute acid.

### Industrial Uses

Although an extremely rare metal only a few years ago, indium has become commercially important. In 1945, the indium content of metal, alloys, and salts produced was 57,434 troy ounces. Production nearly tripled by 1951 and had increased to 153,191 troy ounces. While indium is itself a soft metal, the use of small amounts alloyed with nonferrous metals yields a metal alloy having greater tensile strength and increased hardness, as well as resistance to wear, friction, abrasion, and corrosion. It is used as a decorative metal in silverware where small percentages result in a hard alloy which is said to resist tarnishing. When alloyed with copper, the resulting metal may be highly polished and yields an attractive finish which is not susceptible to oxidation and sulfidation. Its principal commercial use is that of plating aircraft engine and automobile engine bearings, on which it produces a wear-resistant and corrosion-resistant surface. A cyanide bath is usually employed for plating objects with indium. Indium oxide has been used in glass to produce yellow to amber shades.

### Toxicity

While indium is undoubtedly toxic on subcutaneous injection in amounts of from 7 to 30 milligrams per kilogram of body weight (1) or on intravenous injection, it cannot be said to have a sufficiently high toxicity rating to be of any great industrial significance. In animals, large quantities of the hydroxide ingested over a period of 2 weeks are without apparent toxic effect on mice (2). It has been found that the metal and its salts possess no skin irritant properties (1). Weakly acid foodstuffs dissolve indium to some extent from indium-coated containers and ingested indium has been

demonstrated in the urine of animals ingesting indium salts, showing that absorption does occur (3). Vignoli and his associates (4) have investigated the pathological changes produced in white rats following the subcutaneous injection of doses of the citrate or chloride in amounts sufficiently great to produce intoxication. Degenerative changes were found in all cases in the liver, kidneys, and myocardium. The toxic syndrome, when indium is administered in salt form parenterally in experimental animals, includes rapid anorexia, weight loss, nose bleeding, paresis of hind legs, and much twitching. Postmortem examination reveals widespread inflammation and focal hemorrhages (5). When the skin of people were patch tested, there was no evidence of any skin irritant property. It appears that while indium has undoubtedly toxic properties, its industrial use does not constitute a toxic hazard even as a skin irritant.

### Analysis

Indium may be determined gravimetrically by the separation of indium sulfite, ignition, and weighing as the oxide,  $\text{In}_2\text{O}_3$ , (6). A semi-micro method for the determination of indium depends upon its reaction with 8-hydroxyquinoline (7). Indium also gives a red color with alizarin and may be separated by quinalizarin (8, 3). A micro method devised by Royer (9) and depending on electrolytic separation is satisfactorily accurate for amounts of indium in the neighborhood of 1 milligram. The principal spectral lines are 4511.31, 4101.76, 3256.22, and 3039.46.

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## IODINE

### Characteristics

Iodine, I, atomic weight 126.92, melting point 113° C., boiling point 183° C., density 4.948 at 17° C., is a nonmetallic element belonging to the halogen group and consists of bluish-black plates or scales of metallic luster. It sublimes without melting below a pressure of 100 millimeters and may be melted at 1 atmosphere pressure. It is slightly soluble (100 parts of water dissolve 0.02 parts of iodine), soluble in alcohol, carbon disulfide, ether, carbon tetrachloride, chloroform, or iodide solutions. It volatilizes slightly at room temperatures. As the temperature is increased, purple fumes are evolved. While its usual valency is 1, it also is occasionally 3 or 5. Iodine is obtained from the mother liquor of Chile saltpeter and the ashes of seaweeds, and occurs in small quantities widely diffused through nature.

### Industrial Uses

Iodine is used in the aniline dye industry, in the manufacture of iodoform and of aristol (di-thymol-di-iodide), its improved substitute. It is used in the production of pure potassium iodide which is extensively employed in medicine and photography. It is used as a reagent in volumetric analysis, in organic synthesis, and as a catalyst for the

alkalation of primary amines, especially aniline and  $\alpha$ -naphthylamine.

It has been shown that there is a close correlation between the distribution of iodine in surface waters and the incidence of goiter in the United States. The daily iodine requirement for an adult is approximately 0.045 milligram. The thyroid gland is capable of storing excess iodine and for that reason iodine need not be present in the diet daily. Such public health measures as the addition of sodium iodide to water supplies and the use of iodized salt have become widespread. It is used medicinally as an alterative, an antiseptic and caustic, and, because of its opacity to roentgen rays, several of its compounds have proved useful in diagnosis. During 1951, 1,237,922 pounds of crude iodine were consumed in the United States.

The use of triglycerine hydroperiodide for water sterilization in Korea was stated to be especially effective against cysts causing amoebic dysentery. Radioactive iodine has become increasingly important in biological and medical investigations. According to Price and Foege (1) this radioisotope provides a more rapid and generally satisfactory means of estimating thyroid activity than tests of basal metabolic rate. Iodine 132 ( $I^{132}$ ) has a half-life of 2.4 hours and is now commercially available.

### Toxicity

The irritant and corrosive action of iodine is greater than that of bromine or chlorine and is manifested by cough, lacrimation, headache, and vertigo. Certain individuals show an idiosyncrasy towards minute amounts of iodine. The symptoms of iodine poisoning following administration by mouth develop in the following order: gastric uneasiness, disagreeable metallic taste, violent abdominal pain, severe collapse with feeble pulse, diarrheic stools, sometimes bloody. The collapse may be postponed to the second day (2). Iodine and iodides are convertible into thyroxin and in this manner affect the metabolism. The continued administration of iodine compounds may cause irritation of the skin and mucous membranes and may also lead to anemia, men-

tal depression, nervousness, and insomnia. The action of iodine vapor is similar to that of chlorine and bromine, but it is more irritating to the lungs. Henderson and Haggard (3) give the maximum concentration allowable for prolonged exposure as 1/10 of 1 part per million and for short exposure (1/2 to 1 hour) as 0.5 to 1.0 parts per million.

Tests of chronic toxicity of iodine used as tetraglycerine hydroperiodide in the purification of water at an average dose of iodine of 12 milligrams per man per day for 16 weeks and of 19.2 milligrams per man per day for the last 10 weeks failed to disclose any untoward effects on humans (4).

### Analysis

Free iodine imparts a yellow color to an aqueous solution while carbon-disulfide is colored violet, ether or chloroform is given a reddish color, and cold starch solution turns blue. Soluble iodides are readily oxidized to iodine. Insoluble iodides are transposed by hydrogen sulfide, the filtrate containing the halogen. Acidulated solutions of iodates yield free iodine on reduction. The well-known procedure involving titration with sodium thiosulfate is an extremely accurate volumetric method for the determination of small amounts of iodine. However, there are but few colorimetric methods for the detection or colorimetric determination of iodine and none of these is specific. *o*-Tolidine gives a bluish-green color in neutral iodine solutions similar to its reaction with chlorine. Dimethyl-*p*-phenylene diamine also develops a color (in this case red) in solutions of iodine. Bromine and chlorine both yield similar colors.

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## IRON

### Characteristics

Iron, ferrum, Fe, atomic weight 55.85, melting point 1530° C., boiling point 2735° C., is a metallic element having a density of 7.86 at 20° C. Iron is tetramorphous; the transition temperatures between the forms are *alpha* to *beta* 766° C., *beta* to *gamma* 895° C., and *gamma* to *epsilon* 1400° C. *α*-Iron called ferrite, the chief constituent of wrought iron, is a soft, tough, gray-white paramagnetic metal. *γ*-Iron is but slightly magnetic in contrast with the *α*-form. It forms solid solutions with iron carbide and these are present in a metastable state after quenching. Iron is, after aluminum, the most abundant metal and occurs in practically all rocks and in a large number of minerals. It occurs as metallic iron in meteorites and in mineral form as hematite (Fe<sub>2</sub>O<sub>3</sub>), magnetite (Fe<sub>3</sub>O<sub>4</sub>), limonite (Fe(OH)<sub>3</sub>), pyrite (FeS), marcasite (FeS<sub>2</sub>), and siderite (FeCO<sub>3</sub>). Iron forms several series of compounds but is mostly bivalent and trivalent—rarely hexavalent. The first two series of salts are, respectively, those derived from ferrous oxide containing bivalent iron and those derived from ferric oxide or ferric hydroxide which contain trivalent iron. Iron and steel corrode with different degrees of readiness, depending on their composition. Cast iron is often protected by its casting skin. The corrosion of steel is often favored by the presence of impurities which cause electric couples to be established. The electric welding of iron and steel produces fume which contains about 35 per cent of iron calculated as Fe.

### Industrial Uses

Production of iron ore in the United States in 1953 reached a new high of 117,994,769 gross tons. The greater part of this ore was consumed in iron blast furnaces. Smaller amounts were used in steel furnaces, sintering plants and in ferro-alloy furnaces. The pig iron product of the blast furnaces went into steel-making furnaces, with a total steel production in 1953 amounting to 117,821,981 net tons.



## Toxicity

Although ingested ferric chloride has been used with criminal intent to cause poisoning and the absorption of soluble iron salts in quantity is known to produce toxic effects, iron in general is not considered a toxic substance. Iron is chiefly of interest in industrial hygiene in those processes in which workers are exposed to iron oxide fume in welding operations or to iron oxide dust as in the mining of iron ore or in the polishing of materials, such as silver or glass, with rouge. A number of studies of workers' lungs have been made of individuals who had been exposed to iron oxide dust for the greater part of their working life. Collis in 1923 (1) drew attention to certain lung shadows in hematite iron ore miners, which he suggested were produced by iron oxide and not by fibrosis. Doig and McLaughlin (2) in 1936 first described the roentgen appearance of fine nodulation in the lungs of electric arc welders and suggested that these appearances might be due to iron deposits. Enzer and Sander (3) examined 26 electric arc welders who had worked an average of 19 years with metal containing 99 per cent iron and 0.1 per cent free silica and concluded that deposition of iron oxide in the lungs is responsible for the X-ray appearance of nodulation in the lungs. The characteristic marking which makes its appearance after 5 to 10 years' exposure and is revealed on X-ray examination (4) is called "welder's siderosis" by Groh (5). Welder's siderosis was especially considered in a clinical and environmental investigation into the respiratory health hazards of shipyard arc welders made by the U. S. Public Health Service during World War II (6). This condition is of a low order of severity and confirms Sander's and Groh's observations that ordinarily 6 to 10 years are required before diagnosable roentgenographic changes occur. Recently, McLaughlin and his associates (7) have shown that radiographic abnormality in the lungs of silver polishers resulted from deposits of iron oxide without attendant fibrosis of the lungs. Microscopic examination of sections of lung in these cases indicated no evidence of chronic inflammation and particularly no

fibrotic changes. The radiographic stippling or fine nodulation of the lungs with no detectable fibrotic changes seen in rouge polishers has been experimentally produced in the rat by the intratracheal injection of rouge (8). Buckell and his associates (9) radiographed 171 individuals exposed to iron dust in iron turneries. Changes in the lungs in the form of reticulation due to iron oxide were present in 15 instances. In five cases, the individual had been working at this trade for 20 years. The changes were not great, symptoms were few, only one complaining of shortness of breath, although six noted a tendency to cough. Gardner and McCrum, in 1942 (10), showed that in guinea pigs severe pulmonary irritation from welding fumes and gases does not favor infection with tubercle bacilli nor bring about progressive tuberculosis. Prendergrass and Leopold (11) designate the condition resulting from the inhalation of finely divided iron dust from metal grinding as benign pneumoconiosis. It has been stressed by Hunter (12), however, that the lung cannot become a physiological dust trap and yet retain its normal structure and function.

Iron forms several carbonyls of which iron tetracarbonyl,  $\text{Fe}(\text{CO})_4$ , and iron pentacarbonyl,  $\text{Fe}(\text{CO})_5$ , are the most important. The former is a solid consisting of dark green, lustrous crystals which decompose to iron and carbon monoxide at  $140^\circ$  to  $150^\circ \text{C}$ .; the latter is a pale yellow liquid which boils at  $102.8^\circ \text{C}$ . and the vapor of which also decomposes when heated, yielding iron and carbon monoxide. The leakage of carbon monoxide from hot iron stoves has been ascribed to diffusion of carbon monoxide through the iron shell resulting from the successive formation and decomposition of iron carbonyl. Iron pentacarbonyl has been used to some extent in organic synthesis and as a military explosive, which has both incendiary and toxic properties. According to Amor (13), iron carbonyl is somewhat less toxic than nickel carbonyl. The latter is stated to be at least five times as toxic as carbon monoxide (*cf.* Nickel).

## Analysis

Methods for the detection and determination of iron are legion. The separation of iron when present in small amounts by means of cupferron, the ammonium salt of nitrosophenylhydroxylamine, is particularly convenient because the precipitation occurs in acid solution and even in the presence of a considerable amount of mineral acid. Numerous methods have been devised for the colorimetric determination of iron which depend upon the formation of a red color by ferric iron with ammonium thiocyanate.  $\alpha$ ,  $\alpha$ -Dipyridyl is particularly useful for the colorimetric determination of ferrous iron, with which it gives a red color, while ferric iron produces no color change. In the analysis of welding fume samples, the determination of the iron content of the sample is of importance to the industrial hygienist. Keenan and Minderman (14) have recently studied the exact conditions necessary for the accurate analysis of iron in welding fume samples. Their method is furthermore particularly adapted to the range of iron values generally found in samples of this nature.

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## KAOLIN AND OCHRE

### Characteristics

Kaolin is a white, plastic mineral having the composition  $\text{H}_2\text{Al}_2(\text{SiO}_4)_2 \cdot \text{H}_2\text{O}$  and formed by the weathering of feldspar,  $\text{KAlSi}_3\text{O}_8$ . Ordinary sedimentary clay is a less distinctive substance and usually contains many impurities, such as compounds of iron, silica, and carbonates of calcium and magnesium. Ochre is clay colored, with oxides of iron or manganese. A great variety of the mineral earth pigments exists ranging in color from black through brown and red to yellow. The true ochres are low in iron and are yellow, or yellowish brown, and the darker colored mineral earth pigments are those richer in iron. Certain colors are developed by controlled heating of the mineral earths, or such hydrated iron ores as limonite,  $2\text{Fe}_2\text{O}_3 \cdot 3\text{H}_2\text{O}$ , or goethite,  $\text{FeO}(\text{OH})$ , mixed with clay.

### Uses

Kaolin is chiefly used in the pottery industry and in porcelain manufacture. The ochres are paint pigments. The production of mineral earth pigments in the United States in 1951 amounted to 126,432 short tons (1).

### Toxicity

Kaolin and the ochres are ordinarily considered to be physiologically inert and, so far as industry is concerned, of very little hygienic importance. King and his associates (2) for instance tested two types of kaolin



by intratracheal insufflation of this substance into the lungs of rats and compared the lesions formed with those caused by quartz. The kaolins produced only a mild reticulin reaction not comparable with the silicosis produced by quartz. An ignited specimen of kaolin, which contained amorphous silica in the form of glass, produced slightly more reticulosis but no fibrous silicosis. Policard and Collet (3) have found kaolin to be less active in causing fibrosis than mica and considerably less active in this respect than quartz. However, a certain degree of physiological response has been reported by Haubrich (4) with reference to the processing of ochre. Haubrich reports eight cases of pneumoconiosis from ochre dust. Five of these had roentgenologic characteristics of the typical pneumoconiosis caused by ochre dust. The pulmonary markings are minute spots or a network of stippling resembling the pneumoconiosis caused by iron dust. In one case of ochre pneumoconiosis the pulmonary markings had advanced to the third, most advanced, stage. While this type of pneumoconiosis does unquestionably occur, Haubrich states that the incidence is rather minor, as so few are engaged in the process of grinding ochre. Attygalle and associates (5) found that the mild lesions produced by the intratracheal injection of dead bacillus Calmette-Guerin (BCG) were intensified when injected in combination with kaolin.

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## LANTHANUM

### Characteristics

Lanthanum, La, atomic weight 138.92, density 6.16, is a tin-white metal which is malleable and ductile. It has a melting point of 815° C., boils at approximately 1800° C., and burns in air at 440 to 460° C. to form the oxide,  $\text{La}_2\text{O}_3$ . It is the most electropositive of the rare-earth metals. Lanthanum tarnishes rapidly even in dry air. The salts of lanthanum are derived from the colorless basic oxide,  $\text{La}_2\text{O}_3$ , which occurs in a dozen different minerals, such as cerite, parisite, and monazite, usually associated with cerium. Lanthanum, like cerium, adsorbs hydrogen readily. The compound,  $\text{LaH}_3$ , has been described as a brittle, amorphous solid of a bluish-black color. Although lanthanum has been generally ascribed to the rare-earth group of metals, it is now considered to represent a transition stage and cannot be included in the rare-earth series proper (1). Little is known of the alloys of lanthanum. It forms solid solutions with magnesium but not with aluminum (2). A definite metal compound,  $\text{LaAl}_4$ , has been described, however (3).

### Industrial Uses

Lanthanum has few commercial applications. The well-known "flints" for cigarette lighters are brittle alloys of iron, cerium, and lanthanum in various proportions. The oxide is used for the preparation of color-free optical glass and in certain ceramic glazes. Lanthanum compounds are used in cored carbons for special electric arc lamps in lithographic and other printing establishments where an intense white light is needed. Lanthanum oxide is superior to lime for oxyhydrogen lights and has limited application for that purpose.

### Toxicity

Very little investigation has apparently been made of the physiological effects of the salts of lanthanum, but the experimental literature indicates that lanthanum is not distinguished by any pronounced physiological action. The oxalate is said to be prac-

tically nontoxic by mouth even in enormous doses (4), but this is obviously due to the insolubility of this substance. The oral toxicity of lanthanum is very low according to Cochran and his associates (5). In some respects its biological properties are similar to those of aluminum. Bamann (6), however, states that lanthanum salts on intravenous injection act as phosphate acceptors and interfere with blood coagulation by reducing the prothrombin content of the blood.

Some attention has recently been directed towards a source of exposure to lanthanum oxide dust and fume in the lithographic industry where cored arc light carbons containing lanthanum compounds are in use for the intense illumination required. Workers have complained of headache and nausea following the replacement of ordinary carbons with lanthanum cored carbons. While a significant amount of lanthanum oxide fume and dust is evident in such lithographic establishments, no experimental work has been undertaken to prove a causal relationship between the fume and any physiological effects.

### Analysis

Lanthanum is precipitated quantitatively from dilute acetic acid solution by means of 8-hydroxyquinoline when the solution is ammoniacal (7). The precipitate can be dried at 130° C. and weighed or it can be dissolved in 2 normal concentrations of hydrochloric acid and the liberated oxine titrated with an excess of potassium bromate and potassium bromide. The excess  $\text{BrO}_3^-$  is then back-titrated with sodium thiosulfate to an indigo-carmin end point. Small amounts of lanthanum react with quinalizarin to produce a colored lake, and this method may be applied to its detection. However, it should be pointed out that a colored lake formation is not specific for lanthanum since a number of other substances react similarly.

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## LEAD

### Characteristics

Lead, plumbum, Pb, atomic weight 207.22, density 11.34, melting point 327° C., boiling point 1470° C., is a soft gray metal. Lead is heavy, malleable, and ductile, and is protected from corrosion by the formation of a thin coating of gray oxide. Many lead pigments suspended in linseed oil when applied as thin coating form an elastic film on drying which is impervious to water. Depending on its source, lead varies somewhat in atomic weight since it is largely a mixture of isotopes. The end product of the uranium-radium series is lead of atomic weight 206 and of the thorium series 208; the atomic weight of ordinary lead is 207.22. Lead extracted from uranium ores has a density of 11.27 as compared with 11.34 for ordinary lead. Lead is quite resistant to the action of even moderately concentrated sulfuric acid, but is readily oxidized by oxygen in the presence of various weak organic acids, such as acetic acid. The principal lead ore is the sulfide, or galena,  $\text{PbS}$ , and this is generally associated with the sulfides of silver, copper, arsenic, antimony, bismuth, and tin. Other common ores are cerussite ( $\text{PbCO}_3$ ) and anglesite ( $\text{PbSO}_4$ ).

### Industrial Uses

The consumption of refined lead in the United States in 1953 was 1,180,355 short tons in comparison with 1,237,981 short tons in 1950 (1). The amount used in 1953 for storage batteries was 362,767 short tons; for tetraethyl lead 162,443 short tons, for cable covering 146,536 short tons, and for white lead 17,773 short tons. There has been a pronounced increase in the price of lead in



comparison with the war-time price and a decrease in domestic production.

### Toxicity

The economic importance of lead and many of its compounds, taken in relation to its physiological effects, is such that the degree of industrial exposure is of great hygienic significance. In general, workers are exposed to lead fume and dust in the smelting of lead; to lead carbonate, lead sulfate, red lead, and lead chromate in the pigment industry; to lead arsenate dust in the manufacture and use of insecticides; to lead silicate in the pottery industry; to litharge, red lead, and lead peroxide in the storage battery industry; and to the sulfide, carbonate, and oxide of lead in the mining and milling of lead ore. A significant potential lead fume or dust hazard occurs in metalizing with lead wire, in the torch cutting of painted steel (2), and in the streamlining of automobiles. Lead absorption through the intact skin does not occur except in the case of certain lead organic compounds, such as lead tetraethyl. Lead intoxication by inhalation is the most serious mode of exposure in industry, and occurs following prolonged exposure to lead or its compounds. The solubility of the various lead compounds is of more importance than the size of particles, and the rate of solution is not only a function of the surface, but depends also upon the solvent, which in this case is the tissue fluid of the lung (3). Certain lead compounds have been shown to be particularly soluble in fluids of this type (4). The low incidence of lead poisoning among miners in galena mines is probably due to the insolubility of lead sulfide in the tissue fluid of the lungs. Where active absorption of lead occurs in excess of the physiological tolerance, some storage of lead occurs, particularly in the bone tissues. This storage does not, however, occur *pari passu* with the excess of intake but apparently reaches a limiting value.

The diagnosis of lead poisoning still appears to be a matter of some difficulty. No single criterion can be accepted as infallible. With chronic lead poisoning and a clear-cut history of exposure, diagnosis is often simple; with incipient lead poisoning, it is

frequently very difficult to make a true diagnosis of lead poisoning. A number of factors must be taken into account and each of these carefully evaluated, for not only diagnostic skill and experience with lead poisoning are necessary but careful and competent laboratory investigation of the blood picture and of the urinary excretion of lead are also required. The cardinal symptoms of lead poisoning include colic, the lead or Burtonian line, basophilic stippling of the erythrocytes, pronounced urinary excretion of lead, palsy, and anemia. Any one or several of these may be absent. High values of urinary excretion indicate only active lead absorption, but a single low value does not necessarily indicate the absence of lead poisoning (5). Data regarding the urinary excretion of lead by children who have been poisoned by chewing lead paint are of particular interest not only because of the diagnostic value of such data, but also because children tend to store lead more readily than adults. Byers, Maloof, and Cushman (6) found values above 80 micrograms per 24 hours for such lead-poisoned children, while excretion values for a control group were below 55 micrograms per 24 hours.

While the basophilic granulation or stippling of the red blood cells is somewhat limited as a diagnostic sign in lead poisoning, it is nonetheless most useful to an experienced observer. Although it is well known that individuals who have suffered prolonged exposure to lead may exhibit little or no stippling, this basophilic granulation of the red cells when considered with other factors is a valuable index of lead absorption. Belknap (7) considers that more than 12 stippled cells per 50 fields examined in the face of known lead exposure indicates abnormal lead absorption. Lane (8) found punctate basophilia in practically all workers exposed to a lead hazard and has pointed out the significance of the size of the granules. Large granules indicate excessive absorption or mobilization of lead. McFadzean and Davis (9) have thrown further light on the nature and significance of stippling in general and particularly in relation to the anemia of lead poisoning.

Dimercaptopropanol (BAL) therapy was

used for a time in the treatment of lead poisoning and was found to increase the urinary excretion of lead at an early stage of treatment. However its value has been regarded by Belknap (10), by Anderson (11) and by others as debatable. Later investigations with an interesting chelating agent, ethylenediamine tetraacetic acid, have proved more promising in the treatment of lead poisoning. According to Belknap and Perry (12) it does not give the prompt relief of lead colic in comparison with the immediate response to intravenous calcium gluconate, but does stimulate lead excretion markedly. However a combination of these two therapeutic measures is effective in the treatment of lead poisoning. Rieders and his associates (13) have found the sodium calcium salt of ethylenediamine tetraacetic acid especially effective in relieving the symptoms of chronic lead poisoning.

Lead tetraethyl,  $\text{Pb}(\text{C}_2\text{H}_5)_4$ , which is now in common use in motor fuels as an anti-knock substance, is very toxic. Motor grade fuels contain no more than 3 milliliters of lead tetraethyl per U. S. gallon; aviation fuels for commercial use, no more than 4.5 milliliters per U. S. gallon of gasoline. Lead tetraethyl is a clear, heavy, somewhat oily liquid with a peculiar sweetish odor and is somewhat volatile at room temperature. Poisoning from this substance may occur by absorption through the intact skin, as well as by inhalation of its vapor. Lead tetraethyl is lipid-soluble. In poisoning, nervous symptoms predominate. Insomnia, mental irritability, and instability are constant features. Lead encephalopathy with acute mania may develop. In less severe cases, sleep may be broken and restless with terrifying dreams. Visual difficulties are sometimes experienced, anorexia, nausea, and vomiting occur, and weakness, tremor, muscular pains, and ease of fatigue are common complaints. The usual signs and symptoms of chronic lead poisoning may appear. Acute poisoning and fatalities occurred at an early stage in the commercial use of lead tetraethyl, but under regulations promulgated by the United States Public Health Service (14) the danger both of manufacture and use of this substance has been rendered insignifi-

cant. According to Kehoe (15), the lead exposure associated with the handling and dispensing of gasoline containing tetraethyl lead at service stations of the prevailing type in the United States is negligible. In 1933, the United States Public Health Service established a maximum permissible concentration of the lead content of air to which workers are exposed of 0.15 milligram of lead as Pb per cubic meter of air (16). This value has been adopted by the American Standards Association (17) and also by the American Conference of Governmental Industrial Hygienists. However, on the basis of development of clinical symptoms at lower lead concentrations and after careful statistical analysis, Horiuchi and Ida (18) consider 0.15 milligram of Pb per cubic meter in the working atmosphere as too high and they therefore recommend a value of 0.05 milligram of Pb per cubic meter as a safety limit.

### Analysis

Methods for the micro-analysis of lead applying principally to its determination in urine are legion. Practically every means of attack afforded by analytical chemistry has been successively applied or advocated in order to establish a procedure of sufficient merit to be at once rapid and accurate. Spectrographic, colorimetric, polarographic, and volumetric methods have all been advocated for the detection and determination of these minute amounts of lead. Feicht *et al.* (19) have found the polarographic method particularly useful for the determination of lead in environmental samples where the lead exists as an aerial contaminant. The micro-method of Fairhall and Keenan (20) for the determination of lead in biological material is at once rapid and accurate. In this method, advantage is taken of the quantitative segregation of lead by means of diphenylthiocarbazone (dithizone) and a convenient micro procedure which permits the specific identification and quantitative evaluation of micro quantities of lead. The various methods of lead analysis have recently been discussed by Fairhall (21). Sensitive arc lines for the spectrographic detection of lead are



4057.83, 3683.47, 3639.58, 2833.07, and 2614.20.

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## LITHIUM

### Characteristics

Lithium is a silvery-white metal of the alkali metal group, having an atomic weight of 6.940, a valence of 1 and atomic number of 3. It is the lightest of all the metals. Its melting point, variously given over the range 178° C. to 186° C., is probably near 180° C. Its boiling point is 1336° C. and density is 0.534 at 20°. While lithium is widely distributed in small amounts, it occurs principally in epidolite, or lithium mica, 6 per cent; in spodumene up to 6 per cent; and in petalite up to 3 per cent. Lithium is the hardest of the alkali metals and is about as hard as lead. Unlike the other alkali metal phosphates and carbonates, lithium phosphate and lithium carbonate are only sparingly soluble in water. Lithium chloride is fairly soluble in amyl alcohol and in pyridine. Lithium metal readily combines with hydrogen at red heat to form lithium hydride, LiH—a substance that within the last few years has achieved commercial importance and significant applications.

### Uses

Special applications of lithium compounds have accounted for an accelerated production of lithium. The output of lithium in the United States increased from 4,838 short tons in 1949 to 15,611 short tons in 1952. This increase was largely due to the importance of the metal with reference to thermonuclear reactions. Other more commonplace uses for lithium are found in the manufacture of bearing alloys, in optical glass and ceramic glazes, in the manufacture

of radio tubes, and in alkaline storage batteries. The use of lithium chloride in the direct current carbon arc for the suppression of cyanogen bands in spectrographic analysis developed by Keenan and White (1) permits more accurate determination of trace elements whose lines occur in that region.

### Toxicity

Lithium chloride used as a substitute for sodium chloride in certain heart conditions gained some unfavorable attention a few years ago when serious effects were noted in patients using so-called salt substitutes, where a low-sodium diet was prescribed (2, 3, 4). Apparently patients on a low-sodium diet are especially susceptible to the toxic action of lithium chloride. In doses of 1 to 5 grams per day lithium chloride may produce marked symptoms such as muscular weakness, vertigo, tinnitus, blurring of vision, and pronounced tremor. Experimental studies with animals have shown that the intraperitoneal or oral administration of lithium chloride in doses of 1 millimol per kilogram or greater, resulted in diarrhea. Lithium passes more slowly into and out of cerebral tissue than through muscle tissue. There is no evidence of accumulation of lithium in either tissue.

### Analysis

The determination of small amounts of lithium in biological materials by direct chemical means is somewhat difficult, as lithium forms no specific and distinguishing colored compound. However lithium stearate, unlike other alkali stearates, is relatively insoluble in organic solvents and this property has been utilized by Caley (6) for amounts as low as 0.02 milligram. However its spectrographic determination is not difficult. Lithium gives a strong and persistent spectral line at 6707.9 and a weaker, but also persistent, line at 4603.2.

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## MAGNESIUM

### Characteristics

Magnesium, Mg, atomic weight 24.32, is a silver-white metal, with a melting point of 651° C., a boiling point of 1120° C., and a density of 1.74. It is insoluble in water but is dissolved by all acids with the formation of the corresponding magnesium salts. The molten metal burns readily in air, and in the ribbon or finely divided form burns with a bright light to the oxide or nitride giving a continuous spectrum. Although a light metal, magnesium is relatively strong. It is malleable but is ductile only at high temperatures, does not tarnish in dry air but in moist air becomes covered lightly with oxide.

### Industrial Uses

The production of primary magnesium in the United States increased from 6,261 short tons in 1940 to 183,584 short tons in 1943, but it only amounted to 93,075 short tons in 1953. Practically the entire production of magnesium from the early part of 1941 was earmarked for the war effort. In Texas, during World War II, two plants for the electrolytic production of magnesium metal extracted magnesium from sea water. Plants which are located in Michigan used magnesium chloride from well brines, while in Nevada an extensive deposit of magnesite was the source of material used in a large electrolytic plant in Las Vegas. In several other plants, dolomite served as raw material for magnesium production. The most important uses in 1945 were for aircraft structural parts, for rocket launchers, in automobiles and trucks, textile machinery, oil field equipment, automatic tools, sporting goods, household appliances, railroad



equipment, and home construction. There is a demand for magnesium compounds in the refractory field and in caustic-calcined magnesite. Magnesium is used in the manufacture of flashlight powder, signal flares, and pyrotechnics. Industry finds extensive use for alloys such as Dow metal, a trade name applied to a series of alloys containing more than 85 per cent of magnesium. Certain alloys combine high mechanical strength with lightness. Magnesium alloyed with small amounts of other metals is increasingly used in sand castings, die and permanent mold types, and in extruded, rolled, and forged types.

### Toxicity

Attention has been directed to peculiar cutaneous injuries resulting from magnesium alloys implanted in the skin as splinters, slivers, or turnings, and to metal dust which enters a cut or wound resulting, probably, from some other accident. Evolution of gas occurs and this is usually accompanied by local tissue necrosis and occasionally gangrene limited to the locality of the gas tumor (1, 2). Investigation of tissue reaction to magnesium by McCord, Prendergast, Meek, and Harrold (1942) has shown that macroscopic gas tumors may be induced by the subcutaneous implantation of particulate magnesium and high magnesium content alloys. As little as 10 milligrams of powdered magnesium is capable of producing macroscopic tumor masses (3,4). In puncture wounds caused by magnesium, the necessity of removing all the magnesium is apparent since this may lead to a more severe form of injury than the usual ordinary foreign body type. However, according to Gay (1942), magnesium and its alloys are—apart from their inflammable nature—among the most innocuous materials with which workmen come in contact. Gay reports that in his experience of 5 years in the magnesium industry, which included experience with men with approximately 1½ million work days, no time loss has occurred from injury from magnesium splinters (5). Finely divided metallic magnesium does not have the same effect upon the lungs that it exerts in the more dense subcutaneous tissue (Gardner).

The absence of "gaseous tumor" formation is explained by the free communication of the pulmonary air spaces with the external air. Even if manufacturing processes permitted inhalation of an appreciable amount of magnesium dust, it is highly improbable that serious injury of the lungs would ensue (6). Magnesium oxide is one of the substances which in freshly formed fume causes fume fever (7). Fire and explosion is an outstanding hazard in magnesium alloy fabrication plants and especially rigid precautions must be taken to safeguard workers engaged in processing these alloys (8, 9, 10). In addition, occupational health hazards may exist in magnesium alloy foundries from the presence of atmospheric contaminants such as fluorides, sulfur dioxide, carbon tetrachloride, and chromium compounds (11, 12, 13, 14).

### Analysis

While the determination of magnesium itself in dust samples presents no great analytical difficulty, the separation of magnesium from interfering substances requires a considerable amount of care. Colorimetric methods employing 8-hydroxyquinoline, titan yellow, alizarin, curcumin, and quinizarin have been proposed for the estimation of magnesium. Garner (15) has recently developed a colorimetric method for the determination of magnesium in blood or serum by means of titan yellow. After removal of proteins by trichloroacetic acid, magnesium hydroxide is precipitated in the presence of titan yellow. Gum ghatti is used as a stabilizing reagent. Recoveries of  $\pm 0.05$  milligram of magnesium in 100 milliliters of serum are obtainable by this method. According to Averbach (16), the quantitative spectrographic analysis of magnesium alloys can be accomplished with an accuracy of  $\pm 5$  per cent of the contained magnesium. The most sensitive arc spectral lines for magnesium are 2852.13, 2802.71, 2795.54, 3096.92, and 5183.62.

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## MANGANESE

### Characteristics

Manganese, Mn, has an atomic weight of 54.93 and a density of 7.2. It melts at 1260° C. and boils at 1900° C. The pure metal is reddish gray and relatively soft, compared to iron. However, if it contains carbon it is very hard and brittle. The metal tarnishes readily in moist air, especially if it contains the carbide,  $Mn_3C$ , which evolves methane and hydrogen with water. Manganese readily combines with carbon, sulfur, and chlorine; it dissolves in acids forming manganoous salts with the evolution of hydrogen.

### Industrial Uses

The consumption of manganese ore in 1953 amounted to 3,430,095 tons and of this amount 90 per cent was of foreign origin. Although some manganese is used in both the ferrous and nonferrous metallurgical industries, the bulk is consumed in the manufacture of iron and steel. Manganese is considered to be an especially good deoxidizing and desulfurizing agent for steel, this property depending, in part, upon the very slight solubility of the manganese oxide and sulfide in molten iron. Steel containing 12 per cent of manganese is hard and tough and very resistant to shock. Manganese is used in the manufacture of dry cells, in photography, in the manufacture of organic chemicals, in fertilizers, in coloring agents for paints and ceramics, and for bleaching glass. The important compounds of manganese are the oxide,  $MnO$ ; the dioxide,  $MnO_2$ ; chloride,  $MnCl_2$ ; sulfate,  $MnSO_4$ ; and potassium permanganate,  $KMnO_4$ . Manganese dioxide and various manganese salts are added as driers to linseed and other oils. Manganese chloride is used in dyeing; the sulfate is used in calico printing, and manganates or permanganates are used for preserving wood, for bleaching textile fibers, and for disinfecting and oxidizing purposes.

### Toxicity

Industrial manganese poisoning occurs through absorption from the respiratory system following the inhalation of manganese ore dust or fumes from metallurgical processes—particularly the manufacture of manganese alloy steel. The possibility of poisoning through ingestion of manganese is slight. The mining of pyrolusite, grinding, sorting, and loading manganese ores have all contributed cases of manganese poisoning. Manganese is toxic to the respiratory epithelium and exerts a specific chemical action, which in mice results in an intense mononuclear proliferation and infiltration of the lung tissues and, as the action of the manganese proceeds, in cellular death and necrosis (1). Exposure to manganese-containing dust for as short a period of time as 3 months may be sufficient to cause symp-



toms of manganese poisoning, but there is a wide difference in individual susceptibility. The early symptoms of poisoning include languor and sleepiness which precede a complaint of weakness in the legs. A stolid masklike appearance of the face sometimes develops. Marked emotional disturbances such as uncontrollable laughter or weeping occur and there is a peculiar stiffness of the muscles which results in a spastic gait with a tendency to fall on attempting to walk backward or forward (2, 3, 4). The signs and symptoms of chronic manganese poisoning point to involvement of the basal ganglia of the brain. Well-established manganese poisoning cases, in general, fail to respond to treatment. Men exposed to the inhalation of manganese dust suffer a high pneumonia rate. Over the years 1938 to 1945, in one group, for instance, this averaged 26 per thousand as compared with 0.73 per thousand in a control group (1). Van Bogaert and Dallemagne (5) have recently produced manganese poisoning in rhesus monkeys by inhalation of manganese held in suspension by means of an aerosol and have studied the symptoms of this disease and pathological changes produced. Early cases tend to recover or improve if the victim is removed to a manganese-free environment. The importance of early recognition of manganese poisoning is evident. Ten cases of occupational manganese poisoning were reported by Dogan and Beritic (6) and the incidence of manganese poisoning in one mine over a 3-year period was reported by Ueberall (7) as 14.8 per cent. Prevention can be accomplished by ventilation and by preventing the dispersal of the dust or fumes, by enclosed processes, by using mechanical conveyors and local exhaust ventilation.

### Analysis

Although various organic reagents, such as benzidine, 8-hydroxyquinoline, and tannic acid, have been used for the determination of manganese, it is doubtful if any of these surpass in delicacy and accuracy that of oxidizing the manganese to permanganic acid followed by colorimetric comparison

with standards prepared under identical conditions. Either ammonium persulfate or potassium periodate may be used as the oxidizing substance, the latter being in many cases preferable. This method (8, 9, 10) in simplified form may be readily applied to the evaluation of the manganese content of atmospheric dust. Gates and Ellis (11) have developed a microcolorimetric method for the determination of manganese in biological materials with 4,4'-tetramethyldiaminotriphenylmethane. The method is sensitive from 0.02 to 0.5 microgram of manganese per 10 milliliters of solution. Dust counts and particle size determination by improved methods should also be made.

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## MERCURY

### Characteristics

Mercury, Hg, is a silvery, mobile liquid at standard conditions of temperature and pressure. The atomic weight is 200.61, density 13.6, freezing point  $-38.87^{\circ}\text{C}$ ., and boiling point  $356.9^{\circ}\text{C}$ . The metals more or less readily dissolve in or amalgamate with mercury, with the exception of iron and platinum. Mercury forms two series of salts, mercuric and mercurous. The mercurous ion is peculiar in that it is associated into the double ion,  $\text{Hg}_2^{++}$ , not only in solution but in its compounds in the solid and gaseous state. Mercury is constantly giving off vapor and in this manner contaminates the air. At  $20^{\circ}\text{C}$ . the concentration of mercury in air saturated with mercury vapor is 1.84 parts per million, while at  $40^{\circ}\text{C}$ ., the concentration rises to 8.5 parts per million. The degree of atmospheric saturation with mercury vapor depends not only upon the temperature and pressure, however, but also upon the rate of air exchange and amount of surface exposed.

### Industrial Uses

The consumption of mercury in the United States in 1953 was 100,114 flasks of 76 pounds each. Of this amount, 9,408 were used in the electrical apparatus field, 1,865 in the pharmaceutical field, approximately 4,500 were used in the manufacture of industrial and control instruments, and 790 as a catalyst (1). Other uses are in an anti-fouling paint, in the munitions industry, as a disinfectant in agriculture, in the preparation of amalgams, and as a catalyst in chemical processes. It is estimated that there are 80 distinct occupations with potential exposure to mercury and its compounds, and that in the United States in 1940 there were 32,855 persons so exposed (2). Mercury poisoning has been reported among painters engaged in applying anti-fouling plastic paint (3), among men manufacturing fulminate of mercury (4), in scientific laboratories (5), in electrical apparatus production (6), and in the felt hat industry (7). An interesting and rapid development with reference to mercury is the commercial utili-

zation of mercuric oxide in a new form of dry cell, which has important applications because of its long shelf life and supply of electrical energy in proportion to its size.

### Toxicity

It is well known that mercury can be absorbed either through the respiratory tract following the inhalation of vapor or finely divided dust, or through the skin, as well as through the alimentary tract. The clinical picture of mercury poisoning varies with the nature of contact and the type of mercury compound. The most prominent symptoms of chronic mercury poisoning are the psychic disturbance known as erethism (a peculiar form of timidity), tremor (most characteristic symptom though seldom the first to appear), pallor, and stomatitis, which manifests itself by salivation and tenderness of the gums. Acute mercurial poisoning rarely arises in industry and usually results from the ingestion of mercurial salts either by accident or with suicidal intent. Soluble mercurial salts are violent corrosive poisons and are noticeably nephrotic. Brigatti and Baldi (8), following the examination of blood of 88 workmen in different stages of mercurial poisoning, state that true mercurial anemia does not exist. In 1946 Buckell and his associates (9), after examination of 72 men in a workshop where thermometers were being made and 11 men in a chemical works making mercurial compounds, reported that mass observation in these works suggests that most of the workers were suffering from mild degrees of mercury poisoning, but that the symptoms were not such as to produce any disability in the men or any inability to work. Since atmosphere and urine estimations showed that thermometer workers were excreting more mercury than could possibly be absorbed from the atmosphere, absorption of metallic mercury through the skin, or by ingestion through the alimentary canal was considered. A serious outbreak of mercury poisoning in a felt hat factory in Italy in which more than 100 employees were poisoned (Vigliani and Baldi, 10) was finally curbed by the institution of proper physical and medical controls and with no further cases of poisoning. The



use of new carroting agents in the felt hat industry in the United States is eliminating the use of mercury nitrate in the treatment of fur. During the period from 1939 to 1944 a considerable number of cases of acute and chronic mercurialism were found in plants where mercury was used in the heat treatment of tungsten-molybdenum wire and rod necessary for electrical contacts and filaments (11). The manufacture of organic mercury compounds and their utilization as fungicides or for the treatment of seeds has posed new problems with reference to mercury poisoning. Hunter (12) records several cases of mercury poisoning arising from this source. Two deaths of office workers in a warehouse where diethyl mercury phosphate was stored were reported in 1943 (13). The atmospheric content of mercury at the breathing level in the office was found to be 2.7 milligrams per cubic foot of air.

Air containing more than 1 milligram of mercury in 10 cubic meters of air is injurious to health if breathed for long periods of time. In underground mining operations where the ore is associated with free mercury, the problem of controlling mercury vapor is important (14, 15). In the California Mine Safety Orders it is required that sufficient pure air be circulated to provide 100 cubic feet per minute for each man and 500 cubic feet per minute for each animal. The limit above which a hazardous exposure is felt to exist is reached when the urinary excretion of mercury rises to 0.25 milligram mercury per liter of urine (16). Stock (17) estimates the normal daily urinary excretion of mercury to be 0.1 to 1.0 microgram and states that this may rise to several milligrams in persons with amalgam dental fillings or who are in industrial contact with mercury.

### Analysis

Pioneer work by Nordlander in the development of a practical method for measuring atmospheric contamination with mercury resulted in a method which is based on the intensity of the stain obtained when mercury vapor is passed over selenium sulfide paper (18). Woodson later developed a portable detector which utilizes the selec-

tive absorption of ultraviolet at 2537Å by mercury vapor. It has calibrated range of 0.5 to 0.005 part per million (19). An electronic detector for instantaneously determining the concentration of mercury vapor has also been developed which measures concentrations as high as 1 part in 3 million parts of air and as low as 1 part in 200 million parts with an accuracy of approximately 5 per cent (20). Barnes' method for the determination of mercury dust in air sampled by the impinger method permits the separate evaluation of mercuric dust from that of mercury vapor in the atmosphere (21). For the determination of urinary mercury, Storlazzi and Elkins obtained excellent results by using a modification of Stock's method with electrode-deposition of the mercury direct from the oxidized urine (6). To determine mercury in biologic products that had been preserved with phenyl mercuric acetate, merthiolate or other organic mercury compounds, Eckert has developed a method whereby the mercury is determined by means of dithizone (22). Milton and Hoskins (23) have recently developed a chemical method for the determination of urinary mercury, and a method using radioactive mercury of atomic weight 197 as a tracer substance has also been proposed (24). Using this technique, it has been possible to detect  $10^{-8}$  grams of mercury. The reaction of potassium ferrocyanide with nitrosobenzene, which is catalysed by small concentrations of mercuric ion, has been applied to the determination of minute amounts of mercury (25). The concentration of the violet-colored reaction product at a fixed reaction time depends upon the amount of mercuric ion present in the solution. Sensitive arc lines for the spectrographic determination of mercury are 3663.3, 3654.8, 3125.6, 2967.3, and 2536.5. The most sensitive arc spectral line for mercury is 2536.52.

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## MICA

### Characteristics

The micas commonly occur as rock constituents. Chemically, they are complex aluminum silicates combined with either an alkali metal, such as potassium, or with magnesium, ferrous iron, and, in some varieties, lithium, sodium, and ferric iron. More rarely, they may contain barium, chromium, manganese, titanium, and fluorine. They also contain water of constitution. They crystallize in the monoclinic system, but are pseudohexagonal, possess a highly perfect basal cleavage, and are characterized by very strong birefringence. The more common micas are muscovite,  $\text{H}_2\text{KAl}_3(\text{SiO}_4)_3$ ; biotite,  $(\text{H}, \text{K})_2(\text{Mg}, \text{Fe})_2\text{Al}_2(\text{SiO}_4)_3$ ; phlogopite,  $\text{H}_2\text{KMg}_3\text{Al}(\text{SiO}_4)_3$ ; and lepidolite, or lithia mica,  $\text{LiKAl}_2(\text{OH}, \text{F})_2(\text{SiO}_4)_3$ .

Muscovite is transparent and colorless in thin sheets and is distinguished by its highly perfect cleavage and light color. Owing to its transparency and heat resistance, it is sometimes used in stove doors and is then often incorrectly termed isinglass (a fish glue). This mica is not decomposed by sulfuric acid and thus differs from phlogopite and does not give the crimson flame which characterizes lepidolite. It occurs in pegmatite dikes and is found lining cavities in granites. It is also very common in such metamorphic rocks as schist and gneiss. A variety of muscovite, known as sericite, occurs as minute shreds or in very thin veins and is a secondary mineral formed by hydrothermal alteration of silicates, such as the feldspars.

Biotite commonly occurs in irregular, foliated masses. It is usually brown to black, or dark green in color, and even in thin sheets has a smoky color in contrast with muscovite. It is widely distributed, occurring in igneous rocks such as granite or syenite, and is sometimes found in pegmatite veins in large sheets. It is not attacked by hydrochloric acid but is decomposed by boiling, concentrated sulfuric acid.

Phlogopite is distinguished from biotite by its lighter color, weaker absorption, and its decomposition in sulfuric acid. It is, how-



ever, difficult to differentiate sharply from muscovite. It occurs as a metamorphic product in crystalline magnesium limestones and is rarely found in igneous rocks. Lepidolite is a comparatively rare mineral and is chiefly of interest as a source of lithium.

### Industrial Uses

Mica is used in the electrical industries in the form of sheets, washers, tubes and plates, and in a great variety of devices, as in the commutators of d.c. motors and dynamos. For any insulating purpose, as in condensers, and for mounting resistance of electrical heating apparatus, mica can be used. As a transparent material, it is used for stove fronts, furnace peepholes, lamp chimneys, and in warship conning towers. Mica splittings are used in the manufacture of built-up mica products, such as commutator plates, mica cloth, and paper. Scrap mica is used in the manufacture of wallpapers to give them a shiny luster, as a lubricant when mixed with oils, as a fireproofing material, and as a nonconductor of heat. In the United States in 1951, 17,500,000 pounds of sheet, punch, and mica splittings were used. The total output of ground mica in 1951 was 70,122 short tons, of which the roofing industry consumed a major part of the dry-ground mica, and the paint, rubber, wallpaper, and lubricant industries most of the wet-ground product.

### Mica Pneumoconiosis

Although quartz, or silicon dioxide, is well recognized as the etiological factor in producing pneumoconiosis, it was held for some time that silicates were blameless in this regard. However, a type of pneumoconiosis has been found to occur among workers whose only exposure was to mica dust. The U. S. Public Health Service (1), in an examination of 57 men exposed to dust generated by grinding hand-sorted mica which was practically free from free silica, found 10 cases of pneumoconiosis. X-ray examination of 456 men, with more than half of their industrial exposure in the mica field, revealed dust pathology of 9.4 per cent or almost double that in the comparable group with no mica exposure (2). Vestal and his

associates (2) also found dust pathology of 11.4 per cent of an additional 79 workers engaged in handling "clean" mica (mica containing no free silica). Policard (3), furthermore, found that the inhalation of mica dust causes pathological changes in the lungs identical to those produced by the inhalation of silica dust. Ramaswamy and his associates (4) found some degree of nodular formation in the lungs of guinea pigs following the intratracheal injection of mica dust.

### Identification

The identification of the mica group is not difficult owing to the distinctive properties of these substances. The characteristic very perfect cleavage in one direction (001), as well as the strong birefringence, are useful in gross identification. Birefringence is particularly marked on microscopic examination. The extinction angles are very small or practically zero. As stated above, the micas are pseudohexagonal monoclinic. They may be divided into two classes, in one of which muscovite and lepidolite have the optic axial plane normal to (010) and the other parallel. Biotite and phlogopite belong to the latter group. All the micas are optically negative. The refractive index of muscovite, which is 1.58, affords no striking relief but is still evidently much different from Canada balsam. The polarization colors of muscovite are bright pinks and greens and are usually sufficiently distinctive to distinguish this mineral. In the case of biotite, however, the polarization colors are frequently obscured by the absorption color. Talc, which is also probably monoclinic, appears very much like muscovite under the microscope but has a slightly lower refractive index and a little higher birefringence. Mica-quartz particles occasionally appear, but the two minerals may be distinguished by their slight difference of refractive index when tested by the Becke line method (mica has the higher value). Furthermore, the mica portion will usually show a partial, if not a complete interference figure. If the colored ring birefringence of quartz is apparent, this property will contrast with the pale gray-blue or gray-yellow color of the mica. The vitreous luster of the quartz and

the pearly luster of the mica usually are sharply contrasted under reflected light. It may be somewhat difficult to distinguish the various micas microscopically in the examination of some dusts and it is usually quite sufficient to designate them merely as "dark" mica or "light" mica.

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### MOLYBDENUM

#### Characteristics

Molybdenum, Mo, has an atomic weight 95.95, a density of 10.2, and melts at 2620° C. It closely resembles steel in color, is as hard as common iron, and is ductile, tough, and malleable. It is not oxidized easily by air or water at ordinary temperatures. When heated above 600° C., it oxidizes rather readily, yielding white molybdenum trioxide, MoO<sub>3</sub>. The metal dissolves in nitric acid as well as in aqua regia and in concentrated sulfuric acid. The oxides MoO, Mo<sub>2</sub>O<sub>3</sub>, and MoO<sub>2</sub>, are basic anhydrides while MoO<sub>3</sub> is an acid anhydride. Molybdic oxide, MoO<sub>3</sub>, is only very slightly soluble in water, but dissolves readily in alkalis and in ammonia, forming molybdates. Molybdenum alloys have become noted for ability to resist abrasion, lack of failure due to fatigue, retention of these physical properties even at relatively high temperatures, and resistance to corrosion. The benefits of molybdenum as an alloy addition are due to true alloying effects rather than to clearing or deoxidizing action, which is an important function of some alloy elements (1).

#### Industrial Uses

Molybdenum finds its principal use as an alloying element in the iron and steel indus-

try. Smaller amounts are employed in pigments and colors, electrical equipment, lithographing and printing inks, welding rod coatings, and in miscellaneous chemical products. The consumption of molybdenum in the United States rose to a maximum value of 45,644,000 pounds in 1942 but dropped to 26,929,000 pounds in 1945. The molybdenum in high speed steels may amount to as much as 9 per cent, while the molybdenum content of engineering steels does not often exceed 0.3 per cent. Molybdic oxide and cobalt molybdate are both catalysts. Molybdenum resistance wire has been found to be especially valuable in hydrogen furnaces owing to its high melting point.

#### Toxicity

Molybdenum is recognized as having some biological importance for the normal growth and development of certain forms of plant life and has been found to be a normal constituent in minute amounts in tissues and excretions (2, 3). Exposure in industry occurs in certain dusty operations, such as crushing and milling molybdenum ore, heating and rabbling the ore to form calcium molybdate (the form in which it is added to the charge in steel blast furnaces), and in rolling red hot billets of molybdenum steel which give off fumes of molybdenum oxide owing to superficial oxidation. A comprehensive study with particular reference to the possible injurious effect of inhalation of the dust of molybdenum compounds, including also molybdic oxide fume, reported by Fairhall and his associates (4) indicates that the order of toxicity is low both from the point of view of observed clinical effects and from the histopathologic point of view. The inhalation by animals of the dust of molybdenum trioxide, calcium molybdate dust, or molybdenum trioxide fume at an average concentration of approximately 5 milligrams of molybdenum per cubic foot of air proved injurious. No fatalities occurred in animals subjected to molybdic oxide fume for 25 1-hour exposures at an average concentration of 1.5 milligrams per cubic foot of air and only one fatality in 24 1-hour exposures to molybdenite dust at an average concentration of 8.1 milligrams of molybdenum per



cubic foot of air. Analyses of the tissues of animals variously exposed to molybdenum compounds indicate that the greatest storage occurs in the kidneys and bones. Storage, however, is of a transient nature in any of the tissues. Both the absorption and the excretion of molybdenum are rapid. Experiments with the sodium salts of hexavalent chromium, tungsten, and molybdenum have shown that sodium molybdate is less toxic following intraperitoneal injection than either sodium chromate or sodium tungstate in equivalent concentrations. While molybdenum is less toxic in general than several other metals of industrial importance, it is suggested that suitable protection should be insured against the inhalation of any considerable amount of the more soluble molybdenum compounds. In the above experimental study, a useful means of estimation of the extent of absorption of molybdenum was found to be indicated by examination of the blood or urine for its molybdenum content. No toxic effects in workers exposed to the dust and fumes of molybdenum and its common compounds have been reported.

### Analysis

By far the most useful colorimetric method for the determination of small amounts of molybdenum is that involving the estimation of reduced molybdenum. An orange-red color is formed with thiocyanates in acid solution (4, p. 8). Elements of toxicological importance do not interfere with this determination. The concentration of relatively large air samples of molybdenum may be determined by converting the sampled molybdenum to molybdenum trioxide, dissolving it in sulfuric acid, reducing it in a Jones reductor, and titrating with standard potassium permanganate solution. Sensitive arc spectral lines for molybdenum are 3902.96, 3864.12, and 3798.26.

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## NICKEL

### Characteristics

Nickel, Ni, atomic weight 58.69, melting point 1452° C., boiling point 2730° C., density 8.9, is a hard, silver-white metal which takes a high polish. Nickel is divalent in most of its compounds. No trivalent nickel salts are known and the trivalent hydroxide occasionally mentioned in the literature appears to be in reality the dioxide. The metal is malleable, ductile, and very tenacious, harder than iron and does not oxidize in dry or moist air at ordinary temperatures. It forms an unusually large number of alloys of technical importance.

Nickel carbonyl,  $\text{Ni}(\text{CO})_4$ , is a heavy, colorless, volatile liquid formed when carbon monoxide gas passes over finely divided nickel. The reaction of formation is a reversible one, the gas dissociating into carbon monoxide and nickel under varying conditions of temperature, pressure, and humidity. This reaction forms the basis of the Mond process for the refining of pure nickel. Nickel carbonyl has a specific gravity of 1.3185, a melting point -25° C., a boiling point 43° C., and at 60° C., it decomposes with explosion. The vapor burns in the air with a very sooty flame. Nickel carbonyl is soluble in alcohol and in concentrated nitric acid but is insoluble in water. It gives off a peculiar odor which is perceptible when the air contains 1 part of nickel carbonyl in 2 million parts of air. The carbonyls are highly toxic both when injected into the body in the form of liquid and when inhaled as a gas.

### Industrial Uses

A large proportion of the 172,832,432 pounds of nickel consumed in the United States in 1951 entered into the composition of nickel steel and half the remaining amount into other alloys. In addition to its extensive use in stainless steels, nickel is used for the electrolytic coating of other metals, for acid-resisting alloys, for chemical and elec-

trical apparatus, for surgical and dental instruments, as a catalyst in the hydrogenation of fats and oils, and in the manufacture of nickel salts. A certain amount of nickel is used in the cemented carbide tool and die industry and in the production of the new magnetic alloy "Alnico".

### Toxicity

The hygienic significance of nickel with reference to industry has been wholly related to poisoning from nickel carbonyl or to dermatitis produced in individuals sensitive to nickel. The toxic effects of nickel carbonyl are stated by Amor (1) to be at least five times as great as those of carbon monoxide. Armit (2), however, states that 180 parts per million will kill animals after 1 hour of exposure, indicating that it is 10 times as toxic as carbon monoxide. He attributes the peculiar toxicity of nickel carbonyl to deposition of nickel in an extremely fine state of subdivision over the surface of the lungs causing irritation, congestion, and edema. The symptoms of giddiness, dyspnea, nausea, vomiting, and cough which appear immediately after inhalation of the gas disappear rapidly upon removal from its presence. There is no permanent disability in these cases and the affected workman is disabled only for a short time. However, following exposure to greater concentrations, retrosternal soreness, inability to take a deep breath, and a dry ineffective cough and dyspnea develop after a latent period of 12 to 18 hours (1). The depth of cyanosis of the lips and ears is a direct indication of the seriousness of the case. When the degree of asphyxia is severe, the immediate treatment should be that of carbon monoxide poisoning and requires continuous oxygen inhalation. The pathology of this condition has been discussed by Bayer (3). The toxic effect of nickel carbonyl has long been recognized and, as the Mond process is an important means of separation and purification of nickel owing to the ease of preparation and volatility of this substance, effective control measures for nickel carbonyl have been introduced in industry (4). The metabolism of nickel has been investigated by Wase and his associates (5) using the tracer element

Ni<sup>63</sup>. It was found that when the Ni<sup>63</sup> ion is administered it is widely distributed throughout the tissues and organs of the mouse and is rapidly metabolized by the principal tissues, excepting the lungs and brain. Elimination in the urine and feces occurs shortly after administration.

Dermatitis is reported in many industries in which nickel or its salts are used. Cases have also been reported among persons who come in contact with such nickel articles as spectacle frames (6), wrist watches, and suspender buckles. Dermatitis from nickel is a sensitization dermatitis, the worker becoming sensitized by industrial exposure (7). A considerable percentage of those who become sensitized become hardened or desensitized after recovery from the dermatitis. In those cases in which an hypersensitivity to nickel exists, and the person does not become "hardened" by further contact, the condition is ameliorated by removal from contact with the metal or its compounds (6).

### Analysis

The detection and identification of nickel is conveniently made with the reagent dimethylglyoxime which is specific and rather delicate.  $\alpha$ -Benzil dioxime is somewhat more sensitive, and other reagents, such as cyclohexanedione dioxime and  $\alpha$ -fural dioxime, are also useful. Dimethylglyoxime and  $\alpha$ -benzil dioxime, although very sensitive reagents for the detection of nickel in traces, are not suitable for the colorimetric determination of this substance, since they form a microcrystalline precipitate and not a true colored solution. The di-thio-oxalate method developed by Fairhall (8) yields a true colored solution and is especially convenient and accurate for the colorimetric estimation of minute amounts of nickel. Nickel in amounts of 1 milligram may be determined with an average accuracy of 0.02 milligram by this method. Sensitive arc spectral lines for nickel are 3414.77, 3524.54, 3446.26, and 3515.06.

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## NITRIC ACID

### Characteristics

Nitric acid, hydrogen nitrate, aqua fortis,  $\text{HNO}_3$ , is a clear, colorless, fuming corrosive liquid with a characteristic odor. On exposure to light in partly filled bottles it becomes yellowish, due to the formation of oxides of nitrogen. The acid reacts with many metals, giving off brownish-red fumes, is miscible with water in all proportions, and decomposes alcohol violently. Anhydrous nitric acid is a clear, colorless liquid of specific gravity 1.53, melting point  $-41.3^\circ\text{C}$ ., and boiling point  $86^\circ\text{C}$ . It may be prepared by the distillation of a mixture of sulfuric acid and sodium nitrate, by the catalytic oxidation of ammonia, or by the direct fixation of atmospheric nitrogen. The ordinary reagent grade of nitric acid is 68 to 70 per cent hydrogen nitrate. Red fuming nitric acid contains 87 to 92 per cent hydrogen nitrate and dissolved oxides of nitrogen.

### Industrial Uses

The uses of nitric acid in industry are legion. It is of especial importance in organic synthesis, in the manufacture of explosives, celluloid, and nitrates, in metallurgy, and in photoengraving, to mention but a few of the more outstanding uses. The amount of nitric acid produced in the United States in 1953 was 1,764,362 short tons, far exceeding that in 1945 which amounted to only 447,088 short tons.

### Toxicity

Concentrated nitric acid is corrosive and destroys tissues by direct chemical action. In contact with proteins, it forms xanthoproteic acid. It stains the skin and tissues a bright yellow or yellowish-brown, which serves to distinguish it from most other acids. The dilute acid produces a mild irritation and tends to harden the epithelium without destroying it. Continued exposure to the vapor of nitric acid may bring about a chronic bronchitis and more severe exposure may cause a chemical pneumonitis. Treiger (1), in reporting a fatal case of "nitric acid fume pneumonia", states that even though the pulmonary edema, cardiac failure, and broncho-pneumonia are controlled, death results because of pulmonary "fibrosis". The prognosis depends directly upon the concentration of fumes and the duration of exposure. Taeger (2) found that the inhalation of nitric acid fumes not only causes bronchial irritation, but may also have an unfavorable influence on preexistent tuberculosis. The vapors of nitric acid attack the teeth, especially the more exposed front teeth. Long-continued exposure may result in necrosis which spreads to the jaw. The problem of dental erosion in workers exposed to inorganic acid fumes has recently been discussed by Lynch and Bell (3), who found clear evidence of erosion of the incisor teeth in 45 of 126 workers exposed to fume in the nitration of cotton. While no maximum allowable concentration value has been established for nitric acid fume, it is suggested that the amount permitted in workshops should not exceed 10 parts per million of air.

### Analysis

Nitric acid vapor may be absorbed in fritted glass bubblers using dilute alkali as the absorption medium and the nitrate content evaluated by any one of several colorimetric methods, such as the sodium diphenylamine sulfonate procedure (4), the phenoldisulfonic acid method (5), or the 1:3-xylene-4-ol method (6).

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## NITROGEN OXIDES

The common oxides of nitrogen are nitrous oxide  $N_2O$ , nitric oxide (NO), and two forms of the dioxide ( $NO_2$  and  $N_2O_4$ ). In addition, there are the trioxide,  $N_2O_3$ , and the pentoxide,  $N_2O_5$ , which is the anhydride of nitric acid. At ordinary temperatures, the trioxide and pentoxide decompose, and on contact with air, they react in such a way that the principal product is a mixture of  $NO_2$  and  $N_2O_4$ .

### Nitrous Oxide

Nitrous oxide or nitrogen monoxide is a colorless gas, having a slight characteristic odor. Its specific gravity is 1.530 (air = 1). It is not inflammable but it supports the combustion of many substances almost as well as oxygen. It is readily soluble in water at low temperatures. The gas may be liquefied to a thin, mobile, colorless liquid, boiling at  $-88.5^\circ C$ . Metals do not rust in nitrous oxide. Nitrous oxide has no irritating action and is used extensively as an anesthetic for minor surgical operations and dental extractions. Its anesthetic action is rather weak and appears only when the gas is inhaled in high concentration. When inhaled without oxygen, nitrous oxide is a simple asphyxiant. Inhaled in small amounts, it often produces a type of hysteria, hence its common name, "laughing gas". Commercially, it is formed by the decomposition of ammonium nitrate into nitrous oxide and water and is then compressed in steel cylinders under a pressure of about 100 atmospheres. Production of nitrous oxide in the United States in 1944 amounted to 139,760,000 gallons, S.T.P. (1).

### Nitric Oxide

Nitric oxide (NO) resembles nitrogen and oxygen in physical properties. At ordinary temperatures, nitric oxide reacts with oxygen or air to form brown nitrogen dioxide; but the equilibrium is reversed at higher temperatures:  $2NO + O_2 \rightleftharpoons 2NO_2$ . The density of nitric oxide is 1.0366 (air = 1), the melting point is  $-160^\circ C$ , and the boiling point is  $-153^\circ C$ . It is slightly soluble in water, i.e., 4.7 volumes per 100 volumes of water at  $20^\circ C$ . at one atmosphere pressure. Nitric oxide in large concentrations in moist atmospheric air is converted into the dioxide.

### Nitrogen Dioxide

Nitrogen dioxide,  $NO_2$  (and its dimer nitrogen tetroxide,  $N_2O_4$ ) is a white crystalline solid below  $-10^\circ C$ . Between this temperature and  $21.64^\circ C$  it is a liquid, nearly colorless at  $-9^\circ C$ , yellow at  $0^\circ C$ , and at  $21.64^\circ C$ , it is an orange gas becoming reddish-brown as the temperature rises. Within the temperature range of  $150^\circ$  to  $620^\circ C$ , the gas becomes colorless owing to dissociation into nitric oxide and oxygen. This gas is responsible for the yellowish-brown color usually associated with the oxides of nitrogen in air.

### Toxicity

In whatever molecular form nitrogen dioxide is inhaled, it is at once changed to that corresponding to body temperature. At  $40^\circ C$ , approximately 30 per cent of the dioxide is in the form  $NO_2$  and 70 per cent is  $N_2O_4$ . It is in this proportion that the gases act upon the respiratory tract (2). Nitrogen dioxide in the form of  $N_2O_4$  reacts with water to produce nitric and nitrous acids. The dioxide in the form of  $NO_2$  reacts with water and oxygen from the air to produce nitric acid and nitric oxide. These acids react with the alkali salts in the tissues of the respiratory tract forming nitrates and nitrites and in so doing have an irritating action. The nitrates formed have no particular effect, but the nitrites when absorbed exert a systemic action. This action does not, however, play an important part in poisoning by nitrous fumes for the irritation of the respiratory tract is so intense that it obscures the



systemic effect (3). In man, frequently exposed to low concentrations of nitrous fumes, habituation to sodium nitrite is rapidly acquired and prevents the development of systemic effects. The first effect of higher concentrations of the gas may be only that of bronchial irritation. Later the patient may complain of dizziness, headache, and extreme weakness. Several hours after exposure, difficulty in breathing is noted and the patient is "drowned" in his own exudate. The lungs become markedly edematous, death may occur within 24 hours or be delayed for several days (3). Because of its insidious action, it is necessary that anyone who has inhaled a considerable amount of this gas should be removed at once to a hospital for immediate treatment. Fleming (4), in discussing the treatment which can be used during the "symptom-free" interval to prevent development of serious pulmonary edema, reiterates that these patients are suffering from a lack of oxygen, and if this deficiency is supplied, circulation will be maintained and no other medication will be needed. The patient surviving the initial pulmonary edema may develop pneumonia, bronchiectasis, or emphysema as sequelae. Methemoglobinemia may also occur. Nitrogen dioxide is recognized as a potential health hazard in welding operations. The rapid oxidation of the nitric oxide produced in the electric arc to the dioxide is usually assumed. Elkins (5), however, after studying the kinetics of the action arrived at the opposite conclusion: that under the usual conditions most of the nitrogen "fixed" by the arc remains as nitric oxide for some time. In the relatively low concentration of fixed nitrogen present in welding fumes from the electric arc, the predominant oxide present is therefore NO.

In a study of the health of arc welders in steel ship construction made by the Industrial Hygiene Division of the United States Public Health Service (6), it was found that four-fifths of the 2,019 environmental air samples obtained contained less than 10 parts per million of nitrogen oxides. Only 1.8 per cent of the samples contained 25 parts per million or more. It was noted that welders were found to have slightly lower blood

pressure than workers who were not exposed to the welding environment and that the nitrites formed after absorption of nitrogen oxides might possibly be the cause of this minimal clinical effect. Tebbens and Drinker (7) found that 48,500 micrograms of nitrogen oxide was the highest amount produced from one welding rod and from this figure, Viles (8) calculated that only 7.6 cubic feet of air per minute per welder is needed to maintain a concentration below 40 parts per million of nitrogen oxides.

Gray and his associates (9) noted that amounts of nitrogen peroxide exceeding 8 parts per million produce damage in rats and conclude that this concentration would cause injury to man. Experiments by Diggle and Gage (10) indicate that nitrogen pentoxide gas is a lung irritant with a potency of the same order as phosgene. In contrasting experiments with rats using nitric acid vapor as high as 63 milligrams per cubic meter the conclusion was reached that the toxicity of nitrogen pentoxide is not due to the nitric acid formed, but that nitrogen pentoxide reacts directly with a constituent of the pulmonary tissue.

Nitrous fumes occur in the manufacture of nitric acid and in the nitration of cellulose and other organic materials, as in the manufacture of explosives, dyes, lacquers, and certain types of film and celluloid, in the bleaching of cotton and of raw silk, in the metal industry during etching with aqua regia, and also under certain conditions in electric arc welding as noted above. Accidents due to breakage of carboys and other containers of nitric acid are the most common cause of fatal nitric oxide fume poisoning. Exposure of workers to nitric oxide gases frequently occurs in pickling of metal (11), accidents in nitration, cleaning of tanks and towers, decomposition of artificial fertilizer, manufacture of sulfuric acid, and welding with an acetylene torch in enclosures, such as tanks and boilers. A death has recently been reported by Hatt (12) as a result of this latter type exposure.

### Analysis

Mixtures of nitrous oxide, nitric oxide, and nitrogen may be determined in the presence

of one another by combustion with hydrogen or with carbon monoxide in a Drehschmidt capillary (13). Small amounts of the oxides of nitrogen occurring as an atmospheric contaminant may be detected by strips of paper impregnated with Griess' reagent (0.5 gram sulfanilic acid and 0.2 gram  $\alpha$ -naphthylamine dissolved in 200 milliliters of water, with the addition of 150 milliliters of dilute acetic acid). This paper turns pink in the presence of oxides of nitrogen. An application of the Griess reagent method was made by Patty and Petty (14) and has recently been modified by Averell and his associates (15). Quantitative determination of the oxides of nitrogen as an aerial contaminant may be made by the phenoldisulfonic acid method of Piccard, Peterson, and Bitting (16) or the modification introduced by Harrold, Meek, and McCord (17). A careful study of the phenoldisulfonic acid method has been made by Beatty and his associates (18). The method used by the U. S. Public Health Service in the measurement of oxides of nitrogen as an aerial contaminant in shipwelding was a modified version of the Bureau of Mines procedure (18). Flagg and Lobene (19) have devised a rapid method for the determination of nitrogen dioxide in air which consists in absorbing the oxide on silica gel and comparing the color formed by treating with diphenylamine with color standards. Saltzman (20) has recently developed a new specific reagent (a mixture of sulfanilic acid, N-(1-naphthyl)-ethylenediamine dihydrochloride and acetic acid) with high sensitivity and with only slight interference from ozone and other gases, even in tenfold excess.

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## OSMIUM

### Characteristics

Osmium, Os, is a hard, bluish-white metal of the platinum group, having a density of 22.48 and a melting point of 2700° C. It is insoluble in ordinary acids but is readily dissolved by fuming nitric acid, aqua regia, or fused sodium or barium nitrates. It is also attacked by hot fluorine or chlorine. Osmium is harder than glass and is very brittle. The tetroxide melts at 45° C. and boils at 100° C., yielding a poisonous vapor having a pronounced and nauseating odor. Osmium is the only element with a valence of 8 which forms definite compounds.

### Industrial Uses

The amount of osmium imported into the United States for consumption in 1953 was 583 troy ounces with a total of 1,401 troy ounces of new and secondary osmium recovered by refineries in the United States. While the total amount consumed is small, osmium has a variety of useful applications. As a catalytic agent, it causes hydrogen and oxygen to explode at 40 to 50° C. Ammonia can be made with the catalytic aid of osmium from nitrogen and hydrogen at 185 atmospheres and at a temperature of 880° to 1000° C. Osmiridium (osmium-iridium), an exceptionally hard alloy with a high melting point (2700° C.), is used extensively for tipping fountain-pen nibs. Osmium is also used for electrical contacts, for measuring the rapidity of explosion of gun-cotton, and occasionally as the filaments of incandescent lamps. Osmic acid is used as a fat stain in pathological laboratories.

### Toxicity

Metallic osmium is innocuous, but osmium tetroxide has long been recognized as dangerous because of its irritating effect. The restricted use of osmium has confined the number of individuals affected by its poisonous action to a relatively small group. One authentic fatal case reported by Raymond in 1874 resulted from the inhalation of osmium tetroxide which gave rise to a capillary bronchitis. A syndrome described by McLaughlin and his associates (1) caused by the fume of osmium tetroxide during the

refining of osmiridium, consisted of vigorous irritation of the conjunctivae and the mucous membranes of the nose, throat, and bronchi, which is associated in some cases with frontal or orbital headache. The "halo around lights" was a characteristic symptom resulting from the irritation of the eyes. It was temporarily disabling in that the worker was unable to read for about 24 hours. The men engaged in refining osmiridium were exposed to osmium tetroxide in atmospheric concentrations as great as 640 micrograms per cubic meter. No chronic or cumulative effects were noted. The inhalation of osmium tetroxide fume by guinea pigs has been shown by Masturzo (2) to increase the erythrocyte count and to stimulate activity of the bone marrow during intoxication. While at one time osmium tetroxide was used in England for developing finger prints, because of the blackening action produced, this use has been discontinued because of cases of dermatitis resulting from this application. The pathological changes produced in animals by exposure to osmium tetroxide have been recorded and discussed by Brunot (3). In short, the principal effects of exposure are those of ocular disturbances, an asthmatic condition on inhalation, and a dermatitis and ulceration on skin contact.

### Analysis

The most recent method for determination of traces of osmium is that of Sandell (4), which depends upon distillation of the tetroxide and the colorimetric determination of osmium in the distillate by making use of the sensitive thiourea reaction of Chugaev. This method was used in the investigations of McLaughlin and his associates (1).

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## OZONE

### Characteristics

Ozone, an allotropic form of oxygen, is an unstable combination ( $O_3 \rightleftharpoons O_2 + O$ ) in which the liberated oxygen atom possesses great oxidizing power. It is a colorless to blue gas of peculiar odor. In high concentrations it has a characteristic chlorine or sulfur-dioxide-like odor; in lower concentrations, the so-called "electrical odor". Ozone has a specific gravity of 1.62 (air = 1) and will condense at low temperatures to a blue-black liquid (boiling point  $-119^\circ\text{C}$ ). The solubility of ozone in water has been stated to be 20 milligrams of ozone per liter of water at  $0^\circ\text{C}$ . Owing to its powerful oxidizing action, ozone has certain objectionable features, which include corrosion of metals, disintegration of rubber, and the bleaching of dyes and colors. Ozone is prepared industrially by the exposure of air or oxygen to the discharge of high-tension electric currents.

### Industrial Uses

Ozone is used industrially as an oxidizing agent, bactericide, for the production of peroxides, and the bleaching of oils, fats, flour, starch, sugar, and textiles. It is finding important application as a catalyst in oxidative reactions, and when mixed with oxygen often initiates chain reactions. Next to fluorine, ozone is the most active of oxidizing agents. Various other uses, some of which have been questioned, are to counteract odors in occupied rooms, to prevent carbon monoxide poisoning in garages, in water sterilization, and in the control of fungi and spores in cold storage rooms.

### Toxicity

Even in relatively low concentrations (0.1 to 1 part per million), McDonnell (1) found that ozone exerted a powerful irritating action on the mucous membranes of the respiratory organs and, after months of continuous exposure, shortened the lives of guinea pigs. Pneumonia was the immediate cause of death. Higher concentrations lead to death in shorter periods from lung congestion and edema. There is no systemic poisoning as most of the ozone is decomposed on

the mucous membranes of the respiratory tract, where its destructive action is mainly located. Thorp (2) reported that 1 part per million of pure ozone was annoying to 25 per cent of exposed persons but even at 7 hours a day for 5 days did not cause irritation of nose or throat. Witheridge and Yaglou (3) found that concentrations of 0.015 part per million that can barely be smelled by the occupants of a room reduced the smell of body odor sufficiently to permit a reduction of at least 50 per cent in the fresh air requirement for odor control. Higher concentrations were irritating to the mucous membranes of the upper respiratory tract while lower concentrations had no effect on odors. They concluded that the action of ozone on body odors appeared to take place not in the air of the room by oxidation but on the mucous membranes of the nasal passages by masking.

The Heating, Ventilating and Air Conditioning Guide, 1946 (4) states: "The allowable concentrations in the breathing zone are very small, between 0.01 to 0.05 part per million parts of air. These are much too small to influence bacteria. Higher concentrations are associated with a pungent, unpleasant odor and considerable discomfort to the occupants. One part per million causes respiratory discomfort, headaches, depression, and a lowering of the metabolic rate and may even lead to coma."

According to Wilska (5) 0.1 part per million of ozone was found to irritate the respiratory organs after 15 minutes of exposure. Exposure periods of 3 to 4 minutes, totaling 3 to 4 hours per week, produced distinct symptoms of chronic poisoning (shortness of breath, continuous headache) after 2 weeks. Diggle and Gage (6) found the  $LD_{50}$  value for rats exposed for one period of 4 hours to be in the region of 10 to 12 parts per million. Stokinger and his associates (7) found an increased mortality of mice when exposed to ozone mixed with unscrubbed compressed air, as compared with a scrubbed air-ozone mixture. They also state that, contrary to past assertions, no evidence could be found for ascribing the toxic effects of ozone to components of nitrogen oxides in admixture.



While ozone is an oxidizing agent, it could only be expected to have this effect on carbon monoxide when the pure gases are used—not diluted as they both are when applied to garage conditions. In fact, even in the pure, undiluted form the amount of oxidation is small at room temperature. It is usually necessary either to heat the mixture or to pass sparks through the mixture in order to promote the reaction. Goldstein (8) did find that when sparks were passed through a Geissler tube filled with ozone and carbon monoxide at the temperature of liquid air, the spectrum of carbon monoxide gradually disappeared. Clausmann (9) found that when a mixture of ozone and carbon monoxide was exposed to sunlight for 8 days, only 2.8 per cent of carbon dioxide was formed; in darkness, only 0.88 per cent. When it is considered that in these experiments the pure gases were used with only such slight reaction, it could hardly be expected that highly diluted gases would react, although ozone has frequently been advocated for the removal of carbon monoxide. Salls (10) found that ozone generators in operation do not convert carbon monoxide into carbon dioxide at a rate that is fast enough or complete enough to be of any practical use. In a recent survey the Industrial Hygiene Division of Colorado proved by actual tests in garages in which ozone generators had been installed that carbon monoxide was not eliminated (11).

Experimental evidence on the merits of ozone as an aerial disinfectant has led to the conclusion that ozone in concentrations that can be breathed over long periods without irritation cannot be expected to provide any effective protection against airborne bacterial infection through direct inactivation of the infectious carrier particles (12). The Council on Physical Therapy of the American Medical Association (13) found ozone generators unacceptable because of investigations which show that ozone in concentrations sufficient to give an appreciable deodorant action may be harmful to the human body. The figures given for maximum allowable concentration for prolonged exposure by various state and city industrial

hygiene agencies vary between 0.15 and 1.0 part per million of air.

### Analysis

Since ozone is a very reactive oxidizing substance, it may be detected by a variety of reactions, such as the liberation of iodine from potassium iodide solution or the oxidation of a number of substances which yield colors, or it may be identified by other procedures. Unfortunately, several other substances react similarly so that none of these reactions for ozone is specific. In the absence of other oxidizing substances, the liberation of iodine and its subsequent titration with sodium thiosulfate is a satisfactory quantitative method (14). Frequently, however, a colorimetric procedure is advantageous and the oxidation of the leuco-base of fluorescein affords a convenient method (15). The presence of traces of nitrous vapors, carbon dioxide, chlorine, and hydrogen peroxide causes no interference in this latter procedure.

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## PALLADIUM

### Characteristics

Palladium, Pd, atomic weight 106.7, density 12.0, melting point 1555°C., and boiling point 2200°C., is the lightest metal of the platinum group and when pure is very malleable and ductile. It can be beaten out into leaf form. It resists oxidation at ordinary temperatures and remains bright after heating above 800°C. (1). Palladium is characterized by its tendency to absorb hydrogen and when cooled in the gas, will adsorb as much as 935 times its volume (2). Alloys of palladium with cobalt, copper, gold, iron, and silver are known and these together with several other metals appear to form with it an unbroken series of solid solutions.

### Industrial Uses

Palladium is used in calibrating thermocouples for precision thermometry at high temperatures. Certain alloys, such as the silver palladium alloys, are used for electrical contacts, for dental purposes, and in jewelry. To some extent it is used as a catalyst for hydrogenation purposes. Its adsorptive property for hydrogen is utilized by sealing palladium thimbles into vacuum assemblies for the purpose of admitting very pure hydrogen to the vacuum system. Palladium compounds are used to some extent for certain types of electroplating. The amount of palladium imported into the United States has increased markedly and amounted to 227,080 troy ounces in 1953.

### Toxicity

While Hunter (3) found that asthma was caused by the dust of the complex salts of

platinum, he found none of the symptoms of asthma apparent in workers exposed to the much higher concentrations of metallic platinum or to the complex salts of other precious metals including palladium. The dosage of palladium chloride of from 16 to 21 milligrams three or four times daily, formerly recommended in the treatment of phthisis, as well as the use of an emulsion of palladium hydroxide under the name of leptynol injected for the treatment of obesity by Kauffman (4) in dosages of 50 milligrams weekly into abdominal fat, does not indicate that the toxicity of palladium salts is high. Meek and his associates (5) have shown that palladium chloride does not cause skin irritation when applied locally and that the subcutaneous injection of palladium salts can be tolerated in animals without health impairment. Intravenous injection of buffered palladium chloride solution, however, caused toxic manifestations. No cases of industrial poisoning from palladium or any of its compounds have been reported in the literature of industrial hygiene.

### Analysis

Palladium reacts with a number of substances, such as dimethylglyoxime, *p*-dimethylaminobenzylidene rhodanine, and naphthalene-4-sulfonic acid-1-azo-5-*o*-hydroxyquinoline. However, none of these reagents is specific for palladium and it is necessary to remove interfering metals previous to its evaluation. A recent method based upon the reaction between palladous chloride and *p*-fuchsin has the advantage that positive interferences with other metals, and, in particular, those of the platinum group of metals, can be obviated (6). A spectrographic method has been applied by Fothergill, Withers, and Clements (7) to the estimation of the palladium as an atmospheric contaminant. The Pd line 3404.6A is particularly suitable for density measurements.

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## PHOSPHINE

### Characteristics

Phosphine, hydrogen phosphide, phosphuretted hydrogen,  $\text{PH}_3$ , is a colorless gas which may be condensed at a low temperature to a colorless liquid. This liquid boils at  $-87.4^\circ \text{C}$ . and may be frozen to a white solid which melts at  $-133.6^\circ \text{C}$ . The gas has a strong odor resembling decayed fish and is soluble to the extent of about 26 volumes in 100 volumes of water at  $17^\circ \text{C}$ . It is only sparingly soluble in alcohol or ether. It is readily adsorbed on charcoal to the extent of about 5 volumes of gas to 1 volume of charcoal. Phosphine is an unstable gas which can be decomposed by heat alone and which is easily oxidized by oxygen and such agents as the halogens. Phosphine is prepared by the action of alkalis on phosphorus, by the interaction of water and calcium phosphide, or by the action of dilute acids on the phosphides of iron, zinc, tin, or magnesium.

### Industrial Uses

While phosphine is used to some extent in organic preparations, it is not a substance of any great commercial importance. It is shipped in steel cylinders, and is indicated by the Interstate Commerce Commission as dangerous for interstate shipment. Phosphine is of interest to the industrial hygienist not so much because of its manufacture, shipment, and use, however, as because of the fact that it is incidentally evolved as a gas in certain industrial operations, such as the quenching of metal alloys or scoriae with water or in the shipment or handling of ferrosilicon when the material is likely to become wet.

### Toxicity

Phosphine has long been known to be poisonous and dilutions as large as 1 to 10,000 parts of air cause death in a few hours. The effects of prolonged exposure to low concentrations of phosphine have been stated to be somewhat similar to those of phosphorous poisoning, such as embrittling of the teeth and bones. A concentration of 0.2 per cent is rapidly fatal, producing dyspnea, fainting, lowered blood pressure, slowing of the heart, nausea, vomiting, convulsions, paralysis, and coma. Slight cases are said to recover without after effects. Phosphine is said to differ from arsine in that the blood picture is not changed (1). Müller (2) has recently confirmed this and has observed hyperemia in most of the organs and especially the lungs, which became edematous following exposure. He found that with phosphine concentrations of 1:50,000, animals died after two exposures of 4 hours each, and after seven exposures of 4 hours each to 1:100,000. Concentrations of 1:200,000 could be endured by rabbits and guinea pigs for 2 months when inhaled for 4 hours daily. Gessner (3) reported a phosphine fatality when phosphine in quite high concentrations was liberated by the humidity of the air from bags of aluminum phosphide stored in a warehouse and used for fumigating purposes. In a house adjoining the warehouse, 12 persons fell ill with nausea and one of these died. According to Barillet (4), acute poisoning by phosphorus hydrides is possible only by absorption through the respiratory tract. The symptoms of chronic poisoning are anemia and nervous disorders. The proper gas mask filling for phosphorous hydrides according to this investigator is silver permanganate, potassium permanganate, and activated carbon. Unusual cases of phosphine poisoning have originated from cleaning magnesium billets with acid in the manufacture of powdered magnesium (5), from cleaning steel bomb bodies with phosphoric acid (6), and from wet cement used in laying the foundation for a road (7). In the latter case the phosphine probably originated from traces of calcium phosphide in the cement which reacted to form phosphine when water was added.

## Analysis

The exposure to phosphine in industry as noted above is usually a matter of accident rather than exposure to phosphine evolved continuously from manufacturing operations. For this reason, no standard method of evaluation of phosphine as an atmospheric contaminant has been adopted. It may be detected in the atmosphere by the darkening of silver-nitrate-impregnated paper, although the brownish to black color so produced is not specific for phosphine but is also given by certain other hydrides. Heering (8) has advocated the use of mercury-cadmium iodide paper which gives a clear yellow to orange-yellow coloration in concentrations of phosphine of 0.01 milligram per liter within 10 minutes of exposure. Beyer (9) has applied the principle of the Beck and Merres method for arsine to the determination of phosphine in air. Air is passed through a 10 per cent mercuric chloride solution precipitating  $P(HgCl_2)_3$ ; an excess of standard iodine solution is added, and the excess iodine is titrated with standard sodium thio-sulfate solution. At a rate of 600 liters of air per hour, 1 milligram of phosphine per liter of air can be determined. A quantitative method for the determination of phosphine in small concentrations of less than 1 part per million of phosphine in air has been described by Müller (10). In this method the oxidized phosphorus is determined as the blue hydroquinone-molybdate complex (cf. Phosphorus.).

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## PHOSPHORUS

### Characteristics

Phosphorus, P, has an atomic weight of 30.98, a melting point of 44.1° C., and a boiling point of 280.5° C. In addition to the white or yellow form of phosphorus, a number of allotropic modifications exist of which red phosphorus (melting point 72° C., boiling point 350° C.) is the most important commercially. Phosphorus is found in nature only in the form of phosphates of which calcium phosphate and the mineral apatite,  $3Ca_3(PO_4)_2 \cdot CaF_2$ , are used commercially. It forms three main series of compounds of which the trivalent and pentavalent forms are the most important. Phosphorus ignites at 60° C. in air and must be kept covered with water, in which it is insoluble. The characteristic phosphorus odor and pale-green luminescence which is visible in the dark are caused by oxidation of white or yellow phosphorus in moist air to hypophosphorus and phosphorus acids.

### Industrial Uses

The phosphoric anhydride content of the 5,806,723 long tons of domestic phosphate rock consumed in the United States in 1945 was 1,884,035 tons. This high domestic consumption was abnormal, since it reflected a rather high war-stimulated farm income with concomitantly large fertilizer purchases. During the war, the facilities for the production of phosphorus were greatly expanded. During 1945, 68 per cent of domestic phosphate rock was used as fertilizer in the form of superphosphate and 14 per cent was used in the manufacture of phosphates, phosphoric acid, phosphorus, and ferrophosphorus. Production of mined phosphate rock has vastly increased since 1945 and in 1953 amounted to 40,139,000 long tons. Superphosphate is made from apatite



by the action of sulfuric acid on the pulverized rock phosphate. However, phosphoric acid and soluble phosphates are now being prepared on a large scale by the controlled combustion of elemental phosphorus. With a cheapened source of electrical supply, the electrothermic method produces elemental phosphorus on a large scale and at such a low cost that it can be oxidized to phosphoric acid in direct competition with the older acid methods of production.

### Toxicity

Phosphorus poisoning in industry has occurred in waves as the preparation and use of white phosphorus has increased or decreased following the substitution of the less harmful red or amorphous phosphorus, or of the tetraphosphorus trisulfide,  $P_4S_3$ , for the more toxic white or yellow form or as new uses have occurred. The trisulfide has supplanted white phosphorus in the match industry, thus eliminating phosphorus poisoning in that type of manufacture, but there has been increasing use of white phosphorus in the fireworks industry (1) and for war purposes. New methods developed for the reduction of phosphate rock to elemental phosphorus and combustion of the latter to phosphoric acid have again drawn attention to the white form as a potential source of danger in industry. One milligram of yellow phosphorus per kilogram of body weight is usually fatal, while red phosphorus is relatively nontoxic even in comparatively large amounts (2). The exposure to the fumes of phosphorus has long been known to give rise to periostitis and necrosis of the lower jaw. Chronic poisoning occurs slowly following inhalation of fumes and evidence of disease usually begins from a carious tooth or from some lesion of the gum which has become swollen and painful. The bone pathology involved in phosphorus poisoning is characteristic for that disease (3). In spite of the general recognition of the poisonous character of phosphorus, cases of chronic poisoning in industry continue to be reported from time to time (4). Phosphorus burns frequently occur in industry and are often complicated by phosphorus poisoning arising from absorption of phosphorus from the burned area

(5). Immediate flooding with water and prolonged soaking in warm bicarbonate solution is an essential feature in treatment. The affected area should then be washed with a 1 per cent solution of copper sulfate which coats any remaining phosphorus particles with a dark deposit of copper phosphide and makes possible their removal (6, 7, 8).

In addition to exposure to the fumes of yellow phosphorus, poisoning in industry occasionally arises from inhalation of the gaseous hydride phosphine,  $PH_3$ , which is usually accompanied by traces of other hydrides, such as  $P_2H_4$  and  $P_4H_2$ . Phosphine is given off when certain metal phosphides are treated with water and several cases of poisoning have resulted from exposure to this type of gas (*cf.* Phosphine).

Exposure to vapor of phosphorus trichloride, phosphorus pentachloride, or phosphorus oxychloride occasionally occurs in workers in the chemical industry. These vapors act as strong irritants on mucous surfaces, owing to their tendency to decompose in the presence of moisture with the liberation of phosphoric and hydrochloric acids (9). The inhalation of the vapors of both phosphorus trichloride and pentachloride is followed by marked irritation of the nose and throat and this irritation extends to the lung structure which is seriously damaged by any extended contact with high concentrations. The pentachloride is somewhat more toxic to animal life than the trichloride. Henderson and Haggard quote 600 parts per million of phosphorus trichloride as rapidly fatal for short exposure, whereas only 120 parts per million of phosphorus pentachloride were necessary to kill mice with an exposure of 10 minutes. The oxychloride is similar to the trichloride in its action. Dangerous also are the effects of phosphorus trichloride on the skin because of burns. Phosphorus trichloride should be washed from the skin with sodium carbonate. Efficient gas masks should contain soda lime and activated carbon (10). Barillet reports that phosphorus pentachloride is dangerous to a lesser degree and that tetrakisphosphorus trisulfide ( $P_4S_3$ ) is but slightly poisonous. In sensitive persons, contact with tetraphosphorus trisulfide may produce eczema.

## Analysis

Since phosphorus in its oxidized form is relatively inert except insofar as the irritant quality of phosphoric anhydride is concerned, the detection of the reduced forms of phosphorus is chiefly of interest to the industrial hygienist. Phosphorus vapor may be detected by its property of reducing certain metallic salts, such as copper and silver, to the metal form. A method of sampling air contaminated with the vapor of phosphorus has been proposed which depends upon absorption and oxidation of this substance to the pentavalent form and testing for the latter with the usual phosphomolybdate procedure. This, however, is not specific for phosphorus vapor or phosphine alone but will include oxidized forms of phosphorus. The detection of phosphine may be made with silver nitrate paper which turns dark brown after 2 minutes in a concentration of phosphine in air of 1:1 million. Mercuric chloride paper sensitized in 5 per cent potassium iodide solution changes from its original pale yellow color to a reddish-orange color on exposure to phosphine. A filter paper method for the detection of phosphine which differentiates it from arsine has been proposed by Weber (11).

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## PLATINUM

### Characteristics

Platinum is a silver-white metal, crystallizing in the cubic form and having a density of 21.45, a melting point of 1770°C., and a boiling point of 4400° C. Platinum forms two important series of compounds corresponding to the oxidation states, +2 and +4. The metal is tenacious, very malleable, ductile, and softer than silver. Its luster is permanent in air and its coefficient of linear expansion is similar to that of glass. Platinum may be prepared in the form of black powder (platinum black) and as a spongy mass (platinum sponge). It is attacked by the halogens, by fusion of caustic alkalis, alkali nitrates, phosphorus, and arsenical compounds, and may be dissolved in aqua regia and by solutions of alkali cyanides.

### Industrial Uses

The manifold uses of platinum in the chemical and electrical industries are too well known to mention in detail. Platinum is a most important metal if only from the point of view of its use as a catalytic agent. During World War II, a War Production Board excluded platinum for use in jewelry. Platinum during the war was used as a component for spark plugs, magneto and other contacts, and for electronic tubes. The chemical industry in 1953 absorbed 160,622 troy ounces of platinum, while the total output of platinum by United States refiners, representing new and secondary metal, in that year amounted to 76,132 troy ounces. In 1953 the import of platinum reached a new high of 340,632 troy ounces.

### Toxicity

The chief exposure to platinum in industry occurs in the metallurgical and chemical processes of preparation of the metal and its salts. In the preparation of spongy platinum, the sieving process gives rise to the dust of



metallic platinum. However, this dust is of no hygienic significance. The process of manufacture of ammonium chloroplatinate,  $(\text{NH}_4)_2\text{PtCl}_6$ , or the corresponding sodium salts, however, as an initial step in the process of manufacture of spongy platinum gives rise to a certain amount of airborne, soluble complex platinum salts. These substances on inhalation are very irritating. Individuals exposed to dust or spray of complex salts of platinum are subject to running of the nose, sneezing, tightness of chest, shortness of breath, cyanosis, wheezing, and cough (1). Hunter found that 52 of 91 workers exposed in platinum refining works complained of the symptoms noted above. Thirteen of the men were troubled with dermatitis. None of these symptoms was apparent in workers exposed to metallic platinum dust only or to the complex salts of the other precious metals, including palladium. One may safely conclude, on the basis of this investigation, that platinum salts, whether carried as dust or mist, are an industrial hazard and that such aerial contaminants should be carefully controlled.

Further reference to respiratory and cutaneous symptoms on exposure to ammonium chloroplatinate has been reported by Jordi (2) and to chloroplatinic acid by Marshall (3). A recent investigation by Massmann and Opitz (4) disclosed that 12 out of 15 workers exposed to platinum salts complained of symptoms of platinum allergy. Although one would assume that, owing to its great insolubility, metallic platinum is physiologically inert, Sheard (5) reports a case of contact dermatitis which is stated as due to metallic platinum.

### Analysis

Two methods have been advocated by Hunter and his associates for the determination of airborne metallic platinum or platinum salts. The chemical method consists in digestion of the dust sample with aqua regia, the formation of a thallium complex, and the separation of the complexes of all other metals except that of platinum by means of ammonia. The platinum complex is then reduced to the platinous stage by means of stannous chloride and the platinum content

determined by comparison of the orange color of platinous chloride with that of similar standards (1).

Fothergill and his associates (6) collected the precious metals in a silver bead by standard assay methods followed by cupellation and estimation of the platinum and the palladium in the silver bead spectrographically. By means of this latter method, it was found that in a majority of refining operations of platinum, the air content of the factory was in general less than 5 micrograms per cubic meter. High concentrations were found in the handling of dry platinum salts, the highest figure being of the order of 70 micrograms per cubic meter. Sensitive spectral lines for platinum are 3064.71, 2929.79, and 2659.44.

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### PLUTONIUM

#### Characteristics and Industrial Uses (1)

Since 1940, the four transuranium elements immediately following element 92 (uranium)—namely, element 93 (neptunium), element 94 (plutonium), element 95 (americum), and element 96 (curium)—have been discovered as a result of their synthesis by transmutation reactions starting with uranium as the primary material. Of these four transuranium elements, plutonium has assumed the position of domi-

nating importance because of its successful use as the explosive ingredient in the atomic bomb, and of the excellent prospects which it offers as a base material for the development of the atomic energy industry. Plutonium is the only transuranium element for which methods have been developed for production in relatively large amounts—that is, kilogram amounts. Since the whole group of heaviest elements are members of a transition group, this makes the chemical and physical properties of each of the elements of comparable interest.

Plutonium was the second transuranium element to be discovered. The isotope of major importance,  $\text{Pu}^{239}$ , is an alpha-emitter with a half-life of about 24,000 years. The complex nuclear reactions (1 and 2 below), which lead to the production of plutonium in the uranium-graphite chain-reacting units, are as follows: (1)  $\text{U}^{235} + n \rightarrow \text{fission products} + \text{neutrons} + \text{energy}$  (necessary to perpetuate the chain), (2)  $\text{U}^{238} + n \rightarrow \text{U}^{239} \rightarrow \text{Np}^{239} \rightarrow \text{Pu}^{239}$ . The importance of plutonium results from its property of being fissionable with slow neutrons and also to the fact that the problem of its mass production has been solved. The Plutonium Project of the Manhattan District was organized for the purpose of producing this isotope, the explosive ingredient for the atomic bomb. The availability of plutonium, as the result of the successful operation of the chain-reacting uranium piles, has made possible an investigation of its chemical properties. Plutonium has the oxidation states VI, V, IV, and II and there is a shift in stability toward the III state. Numerous compounds have been prepared and their properties determined. Since plutonium has the relatively high specific alpha-radioactivity of about 140,000,000 alpha disintegrations per minute per milligram, special equipment and special precautions are necessary in the investigations of its properties. One microgram of plutonium equals approximately 1/16 microcurie. Plutonium has been experimentally found to exist in nature in minute amounts. In 1942, Seaborg and Perlman found plutonium in pitchblend in an amount corresponding about 1 part to  $10^{14}$  and Garner,

Bonner, and Seaborg found a comparable amount in carnotite.

### Toxicity

The radioactive metals involved in nuclear fission present a danger to those working in production plants and laboratories. As a result of the hazards created by plutonium production, numerous and extensive medical and biological studies were incorporated with the Plutonium Project in an attempt to ascertain the maximum permissible exposure, the matter of minimal injury, latent injury, reliable biological indices, cure and causes of death for which there were little experimental data (2).

Brues and associates (3) and Lisco and associates (4), in a study of carcinogenic action of some substances which may be a problem in certain future industries, determined that when plutonium ( $\text{Pu}^{239}$ ) was injected intravenously, it becomes most concentrated at first in the liver and spleen and then is later translocated to bone. The liver is damaged but is without tumor formation. A parallel is drawn to the commonly used diagnostic substance thorotrast. In addition to splenic atrophy and gross liver changes, the other symptoms of acute plutonium were similar to acute total body radiation sickness. Chronic effects of exposure to plutonium involved the local graying of hair, progressive liver damage, and bone sarcoma. After subcutaneous injection of 1 microgram of  $\text{Pu}^{239}$ , local fibrosarcomas appeared within 1 year, and local epilations, ulceration, keratoses, muscle destruction, and atrophy also occurred. A high percentage of local fibrosarcomas were noted following both the subcutaneous and intramuscular injections. Because of its affinity for collagenous tissues, plutonium bone tumors are more common in the spine.

Hamilton (5) observed the metabolic patterns of the fission products and actinide elements following parenteral administration and noted the predilection of these substances for prompt deposition and prolonged retention in the skeleton. These elements localize in and adjacent to the osteoid matrix (not in the mineral structure) and can



readily irradiate the marrow cavity. For this reason, according to Hamilton, plutonium alpha particles are more dangerous to the blood-forming tissues than those of radium.

Studies using rats indicated that unlike radioactive strontium, plutonium is not more rapidly deposited in the bones of young and calcium deficient rats; also, unlike strontium, plutonium does not follow the path of calcium metabolism but is deposited in uncalcified bone matrix (6). In experimental work at the Argonne National Laboratory, it was found that after rats and a dog had received intravenous injection of plutonium from 2 hours to 5 months previously, the administration of nontoxic doses of zirconium dissolved in sodium citrate markedly increased the urinary excretion of plutonium (7). The zirconium displaced the plutonium first from the liver and later from the bones. Investigation of different dose levels by Schubert and White (8) indicates that there is an increase in the urinary excretion of plutonium in rats which is proportional to the dose of zirconium. Foreman and associates (9) found that the administration of calcium ethylenediamine tetraacetate accelerates the excretion of plutonium in humans, particularly when given shortly after plutonium has entered the body.

The maximum permissible concentration of  $\text{Pu}^{239}$  in air for continuous exposure is 0.001 microgram per cubic meter. The life time tolerance dose is 1 microgram of plutonium fixed in the body. The "General Rules and Procedures Concerning Radioactive Hazards" of the Isotopes Branch of the United States Atomic Energy Commission (10) include the following statements:

"The tolerance level for total or limited body exposure is 0.1 rem (roentgen equivalent man or that quantity of radiation which when absorbed by man produces an effect equivalent to the absorption by man of one roentgen of X or gamma radiation). No individual shall knowingly expose himself or cause others to be exposed to more than 0.1 rem in any 24 hour period. No work with plutonium in any chemical or physical form is even to be done by a person having a break

in his skin below the wrist. No exposed plutonium is even 'tolerable'; the following are maximum levels which are perhaps unavoidable in some cases. For spills and contamination levels for exposed surfaces, floors or bench tops on a small spot, the maximum level is 2,000 decompositions per minute; for a large area, 14,000 decompositions per minute per square foot. Any work with materials susceptible to atmospheric distribution of plutonium (that is, dusting, spillage, vaporizing, effervescence of solution) shall be done in an adequate hood. All discarded material which has been liable to plutonium contamination is to be buried. Distinctive cans are to be provided and these handled with proper discretion."

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## PORTLAND CEMENT

### Characteristics

A combination of limestone with clay or shale is the predominant raw material for making Portland cement and, in 1945, 71.4 per cent of the output was made from this combination of raw materials. Cement rock and limestone were the raw materials used in 19.8 per cent of the cement; blast-furnace slag and limestone accounted for 6.8 per cent. The limestones used usually contain a small but variable quantity (between 3 and 11 per cent) of free silica as chalcedony or quartz. In the shales the quartz values range between 19 and 36 per cent, and in the clays between 11 and 24 per cent (1). The raw materials are transported from quarries to a crusher house where they are broken into sizes convenient for grinding. Proper proportions of the different rocks are then reduced to a fine powder in mills by either a wet or a dry process. The mixture is calcined in rotary kilns at a temperature of 2700° to 2800° F. and the resulting clinker is cooled and reground with a small amount of gypsum to control the rate of setting. The aspects of the chemistry of clinker formation, the phase equilibria of clinker components, and the phenomena involved in hydration setting and hardening have recently been described by Bogue (2).

### Industrial Uses

The production of Portland cement, which constitutes about 99 per cent of the total output of hydraulic cements produced in the United States, amounted to 250,821,410 barrels in 1952 and was more than double the production (106,353,595 barrels) of 1945. In addition to its enormous utilization for building construction and road building, Portland cement is extensively utilized in industry for a variety of purposes, such as lining pipes used in oil fields, submarine construction, and the manufacture of drain pipes, molds, and facings. Cement has increasing use for grouting railroad ballast to increase stability and reduce track maintenance expense.

### Toxicity

The manufacture of Portland cement is essentially a dusty process and employees at different parts of the cement plants are frequently exposed to heavy concentrations of this dust. Owing both to the nature of the dust and the extent of exposure, several studies have been made of the health of workers in this industry. The U. S. Public Health Service in 1928 (3) made such a study in which 570 men (active employees or previous employees in a single plant) were examined. As a result of this study it was felt at that time that inhaled cement dust produces an asymptomatic pneumoconiosis. They stated that although "frequency of the minor respiratory diseases was found to be high among the cement workers, the more serious respiratory diseases, such as pulmonary tuberculosis and pneumonia, caused relatively little disability among these workers". In 1938, the Portland Cement Association (4) published a report of sickness absenteeism and mortality in 81 plants employing a total of 14,148 men. There was no evidence of unusual amounts of chronic respiratory illness in this group. This was also confirmed by the extensive study made by Gardner and his associates (1) in the following year. Gardner surveyed 17 widely distributed plants comprising 2,278 employees. While this survey indicated the presence of a high concentration of dust in the atmosphere of the finishing mills and packing departments, this dust was found to contain but very little free silica. In the raw mills the dust was found to contain from 1 to 30 per cent of silica. A study of the health of the workers, with emphasis on roentgenographic examination, indicated that only eight out of 2,278 employees showed evidence of nodular fibrosis attributable to dust and that in six of these, previous exposure to silica dust in previous employment was presumably responsible for this condition. In general, Gardner considered that, compared with the dust hazards in hard-rock cutting, mining, and other silica industries, the problem in the cement industry is trivial. The incidence of tuberculosis and other chronic affections of the lungs was found to be less



than in the general population, and it was concluded that prolonged inhalation of cement dust has no unfavorable influence upon susceptibility to tuberculosis infection or upon its subsequent evolution. Marchand (5), in a review of the various products which may produce perforation of the nasal septum as an occupational disease, lists cements among other hygroscopic materials. Baetjer (6) has recently added significantly to our knowledge of the problem of exposure to cement dust by studying the effects of exposure of animals to cement dust under carefully controlled conditions. This investigation was made with particular reference to the question of susceptibility to lobar pneumonia following such exposure. Exposures varied in duration of from 1 day to 30 weeks and high concentrations of Portland cement dust were used. The animals were inoculated with Type I pneumococcus suspension intrabronchially. This investigation showed that exposure to high concentrations of Portland cement dust does not lower resistance to lobar pneumonia, and, furthermore, in the animals studied there were no apparent acute or chronic pathological changes in the lung tissue following such exposure. These animal experiments support Baetjer's conclusion that although pneumonia rates were considerably higher in all of the Portland cement plants taken together than in other industries, there was a marked difference in the pneumonia rates among cement workers in various parts of the country, and, when further comparison was made between those cement plants located in similar geographic areas with those of other industries, the pneumonia absenteeism rates were approximately the same in the two groups.

In 1950 Jaeger and Pelloni (7) found that the dermatitis occasionally occurring among cement workers was due to traces of soluble chromates in Portland cement and this finding has been confirmed by several later investigators (8, 9, 10, 11). Denton and associates (11) found the water-soluble hexavalent chromium content of the first washing of Portland cement to vary from 0.03 to 6.9 micrograms per gram of the original cement.

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## RADIOACTIVE SUBSTANCES

It is beyond the scope of this discussion to cover even briefly the vast accumulation of information concerning radioactivity in general, including such current problems as the biological effects of atomic warfare, shielding and radioactive fall-out—the term applied to the tons of radioactive soil and debris taken up into the atmosphere by a surface, or near surface, blast. This section is therefore limited to a brief discussion of industrial exposure.

Radioactivity is characterized by the emission of three types of radiation known respectively as alpha, beta, and gamma rays. These three radiations resemble anode rays, cathode rays, and X-rays, respectively. Alpha rays are particles of helium carrying

two unit positive charges and having a velocity of 5 to 7 per cent as that of light. Beta rays consist of electrons shot off from the interior of radioactive atoms with velocities up to that of light. Gamma rays are the most penetrating—so penetrating, in fact, that gamma rays may be detected from 30 milligrams of radium after passing through 30 centimeters of iron. From radioactive evidence up to 1940 there appeared to be about 40 radio-elements. Since that date this list has been greatly extended. Certain of these have identical chemical properties which, although differing slightly in atomic weight, are called isotopes. For instance, radium of atomic weight 226 and mesothorium-1 of atomic weight 228 are identical chemically and are known as isotopes.

Apart from its use as a curative agent, radium is becoming more important industrially for the radiography of castings and machine parts to detect such flaws as blow holes and "pipes" because the penetration of gamma rays is more pronounced than that of X-rays. Both radium and mesothorium, but particularly the latter, are mixed with phosphorescent zinc sulfide to make luminous paint, which is extensively used for watches, clocks, gauges, and other indicating dials. Radon and thoron are evolved from these two substances, respectively, and are both radioactive. Physical contact with these radioactive substances, ingestion or inhalation of radioactive dust, inhalation of gaseous emanation, or exposure of the whole body to gamma radiation results in severe injury (1, 2, 3). Numerous devices and protective equipment have therefore been devised to protect workers (4-10). A radium tolerance dose of 0.1 microgram has been tentatively established by the National Bureau of Standards for humans. Routine samples of exhaled air are recovered from workers and it has been shown that the exhaled breath will contain 1.1 micromicrocuries of radon per liter for each 0.1 microgram in the body (11). Hoecker (12, 13) has recently shown that a more exact figure may be obtained from measurement of the Rn/CO<sub>2</sub> ratio of output. The maximum allowable amount of radium "fixed" in the body, *i.e.*, the amount which has been in the body 2

years or more is 1/10 microgram. If the radon content of the air of workrooms exceeds the adopted tolerance limit of 10<sup>-11</sup> curie per liter, a search should be made by means of a Geiger-Müller counter to locate the contaminant, which should be promptly removed.

While radium itself is not poisonous in the usual physiological sense, the harmful effects are produced by radiation. Because of its relation to calcium, it can replace or is deposited with calcium in the bones and exercises destructive effects on the tissues as a result of its disintegration products. In small doses the destructive effects are frequently only noticeable after a considerable length of time—sometimes as long as 10 years. The destructive action of radium activity results in lung carcinoma, osteogenic sarcoma, blood dyscrasia, and skin injury. This has occurred where large deposits of from 12 to 100 micrograms of radium in the body have accumulated. Unfortunately, when radium is once deposited in the bones, it remains there almost indefinitely and cannot be removed by medical treatment. Such deposits will not occur if standard recommendations for the protection of workers are followed.

The radon concentration in the atmosphere of workrooms should not exceed 10<sup>-11</sup> curie per liter and the whole body exposure of the workers to gamma radiation should not exceed 0.1 roentgen per working day in order to insure safety. Furthermore, proper precautions should be taken against the inhalation or ingestion of radioactive dust. Cowie and Scheele (14) have discussed in detail the precautions to be observed in handling radium and have pointed out the inadequacy of protection against X-rays in most hospitals. Wirth (15) has recently discussed the necessary safeguards and precautions to be used in the handling of radioactive material (*cf.* Plutonium).

The problem of personnel protection in atomic products operation is a specialized field. About 9,000 men and women are engaged in producing plutonium (16) in one plant. In view of the fact that large quantities of radioactive materials have been processed in this plant over a period of 10 years, during which no injury due to radia-



tion has occurred, this constitutes an outstanding example of the effectiveness of a program of careful industrial control. The few following selected references (17-22) may be of further interest with reference to industrial exposure.

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## RUBIDIUM AND CESIUM

### Characteristics

Rubidium, Rb, atomic weight 85.48, density 1.53, melting point 39.0° C., boiling point 679° C., and cesium, Cs, atomic weight 132.91, density 1.9, melting point 28.4° C., and boiling point of 690° C., are both members of the alkali metal group. These are silver-white, very soft metals. Both decompose water vigorously, becoming ignited, and they both resemble potassium closely in their chemical properties. Rubidium salts impart a brilliant red color to the nonluminous flame, while cesium colors it violet. Rubidium gives off a green vapor when heated. One of the most important sources of rubidium and cesium chlorides is the mother liquor remaining after the extraction of potassium chloride from carnallite. Cesium is active photoelectrically. An isotope of rubidium, Rb<sup>87</sup>, which occurs naturally, emits beta radiation. The isotope of cesium, Cs<sup>137</sup>, a gamma emitter having a half-life of 33 years, has limited application in radiation therapy.

### Industrial Uses

Cesium has recently been found to have important uses in the construction of photoelectric cells (1) and the use of these cells for accurate temperature indication for forging, extrusion, and casting purposes is growing. In addition to its use in thermionic valves, cesium, as the oxide, is used to a limited extent in ceramics. An interesting and important use of cesium during the war has recently been disclosed, *i.e.*, its use in a cesium vapor lamp which emits infrared radiation (2). The infrared radiation en-

abled secret two-way conversation over an invisible search light beam which, unlike radio, precluded "jamming" or eavesdropping. While rubidium is not extensively employed in industry, it is of some importance in the manufacture of photoelectric cells. Both rubidium and cesium have been used in industry as catalysts for the polymerization of certain resins used in coating materials.

### Toxicity

While rubidium and cesium have been shown to have pronounced physiological action in experiments with animals, the toxicity of their various compounds is of minor importance in industry. Hyperirritability including marked spasms has been shown to follow the administration of rubidium or cesium in amounts equivalent to the potassium content of the diet (3). Follis (4) found that the survival time for rats fed cesium salts was somewhat less than that for those fed rubidium salts, confirming the earlier work of Mitchell. The latter found in addition that replacing the potassium in the diet by an equivalent amount of rubidium or cesium was followed by death of rats after 10 to 17 days. When injected subcutaneously, Graham and Wright (5) found that 85 per cent of the cesium excreted by mice was excreted by the kidneys. Of the injected cesium, 17.5 to 20 per cent was excreted the first 24 hours and 3 per cent the second 24 hours. When rubidium was injected, the first day's excretion of the rabbit was divided between the feces and urine in the proportion of 5 per cent to 95 per cent (6). Sheldon and Ramage (7), by spectrographic studies, found that rubidium is widely distributed in the body and is particularly present in the heart and skeletal tissues, while Scott and Canaga (8) found cesium to be localized in the retina.

### Analysis

The analytical determination and separation of both cesium and rubidium involves considerable difficulty and is still a major problem in analytical chemistry. Potassium salts usually interfere seriously. The precipitation of rubidium as the silico-tungstate

( $\text{SiO}_2 \cdot 12\text{WO}_3 \cdot 4\text{Rb}_2\text{O}$ ) has been proposed by Freundler and Ménager (9) and has been claimed to be accurate if the ratio of rubidium to potassium or sodium is greater than 1:40. According to Dutt (10), cesium may be precipitated from its solution as  $\text{Cs}_2\text{NaLa}(\text{NO}_2)_6$  by a 50 per cent solution of  $\text{Na}_3\text{La}(\text{NO}_2)_6$ . After washing with cold methyl alcohol, the crystals can either be dried and weighed or the nitrite can be determined volumetrically by titration with acidified  $\text{Ce}(\text{SO}_4)_2$  solution. The spectrographic method for the determination of rubidium has been used in its determination in plants (11), in soil (12), and in animals (13). The most persistent—not necessarily the most sensitive—arc spectral lines for the determination of cesium are 4593.2, 4555.3, 4538.9, and 2525.6. The rubidium lines are not particularly persistent, with the exception of 4571.7.

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## SELENIUM

### Characteristics

Selenium, Se, atomic weight 78.16, is a nonmetal which has certain metallic properties. The density is 4.8. It melts at 217° C. and boils at 688° C. Like sulfur, it exists in a number of allotropic forms and the vapor varies in molecular species from  $\text{Se}_8$  to  $\text{Se}_2$ . It has valencies of 2, 4, and 6. The electrical conductivity of the gray form is poor but it is greatly increased on exposure to light which makes this form of selenium useful in the construction of apparatus for the measurement of light intensity. It is precipitated from its solutions by sulfur dioxide and it is less active than sulfur, both as a reducing agent and as an oxidizing agent.

### Industrial Uses

The production of selenium in the United States in 1940 amounted to 328,731 pounds and rose to 635,581 pounds in 1943, but dropped in 1945 to 542,099 pounds. Production in 1951 was 457,004 pounds. Its principal sources are the flue dusts of processes in which sulfide ores are roasted and anode slimes formed in the electrolytic refining of copper. By far the greater amount of selenium is absorbed by the glass industry while smaller amounts are used in rubber manufacture and in photoelectric cells. In the production of stainless steels and of commercial copper, selenium is used as an alloying element to improve the machineability of the metal. During the late war an important use was found in the application of selenium cells for the detection of incendiary bombs. Another use depends on its application to the manufacture of rectifiers. At present, about 100,000 pounds of selenium are used yearly for decolorizing glass (to neutralize the greenish tint due to iron compounds), for producing pink, ruby, and black glass, and for colored glazes (1). It finds a limited application in the production and coloring of plastics and in paint and ink pigments.

### Toxicity

The literature regarding the toxic effects of ingested selenium is extensive because of

the disastrous effects of small amounts of selenium occurring in grain and herbage consumed by livestock in western states of the United States. A survey of the rural population in these same areas had disclosed a number of symptoms attributed to selenium intoxication, together with definite proof of urinary excretion of selenium (2). While the question has been raised whether the garlicky odor in the breath of animals which have ingested selenium compounds may not be due to a trace of tellurium as an impurity, McConnell has shown definitely by means of radioactive selenium that 3 to 10 per cent of the original amount of selenium subcutaneously injected was exhaled within 24 hours (3). The nature of the volatile selenium compounds exhaled has not been definitely settled, although it is generally assumed that they are di-methyl selenides or analogous substances. Hydrogen selenide is highly toxic as shown by animal experiments (4). Rats fed selenium in a grain diet at concentrations of 3, 5, 7, 10, 20, and 40 parts per million showed toxic effects at all levels of selenium. A concentration of 10 parts per million killed most of the animals within 8 weeks. Lower concentrations produced chronic symptoms, which included a decreased growth rate, a restriction of food consumption, and slight to severe pathological lesions (5). In man, a concentration of 0.005 milligram per liter is intolerable, producing eye and nasal irritation. The experimental work of Dudley indicates that the pathological changes following exposure to hydrogen selenide refer to a chemical pneumonitis which may persist in a subacute form together with fatty metamorphosis of the liver which tends to decrease with time. This is accompanied by a progressive change in the spleen. In industry where workers have been exposed to selenium in copper refineries, a number of symptoms, such as pallor, gastrointestinal disturbances, nasal and throat irritation, garlicky odor of breath and perspiration, metallic taste, and nervousness, as well as the urinary excretion of selenium, have been reported (6). An instance has recently been reported in which workers engaged in melting aluminum scrap contaminated with se-

lenium were exposed to high concentrations of selenium fumes (7). Several workers were acutely affected but all recovered within 3 days and there were no sequelae. Buchan (8) has also recently described five cases of industrial selenosis due to exposure to less than 0.2 part per million of hydrogen selenide. The symptoms were predominantly those described above. While contact with metallic or amorphous selenium has not been reported as a source of skin injury, cases of dermatitis have been reported following exposure to selenious acid and certain of its salts (9, 10). The maximum allowable concentration of hydrogen selenide should be lower than that amount which produces eye or nasal irritation. This would require that the degree of contamination should be less than 1 milligram per cubic meter.

### Analysis

The identification of selenium is greatly assisted by the volatility of certain of its compounds which permits separation from a number of interfering substances. Among the reagents which facilitate its detection are 1,8-naphthylenediamine sulfate, pyrrol, and codeine sulfate. The procedure adopted for the determination of selenium in biological material by Dudley (4) depends upon the oxidation of selenium to the hexavalent condition by means of free bromine in the hydrobromic acid solution. The free bromine is removed by distillation and selenium may then be distilled from the bromine-free hydrobromic acid. The selenium content of the distillate may be determined by reduction with sulfur dioxide or hydroxylamine hydrochloride. The pink-colored residue obtained on the filter paper by filtration of such a reduced mixture serves to indicate the presence of selenium qualitatively and, when present in quantity, the selenium content may be determined by filtration through an asbestos Gooch crucible and weighing. The colorimetric determination of selenium by means of pyrrol is said to be applicable to a quantity of selenium amounting to 0.0005 milligram in a concentration of 1:1,000,000.

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## SILICA

Silica ( $\text{SiO}_2$ ) or silicon dioxide, is the most abundant of all the minerals and rocks that form the earth's crust. It is characterized by its hardness and chemical resistance to reagents. It is slightly soluble in alkalis but the finely particulate material is only very slightly soluble in water (1, 2). Silica fractures into very minute particles. In the crystalline form it occurs as quartz but two other forms are known. These are tridymite and cristobalite, and each of these exists in a number of modifications. Sand, flint, and agate are familiar forms of silica and diatomaceous earth, which is occasionally found in nature in large deposits, is composed of the silicious skeletons of diatoms. In view of what is known about the disease called "silicosis", it is important to distinguish between silica in the free state, as  $\text{SiO}_2$ , and silica in the combined state, such as the various silicates. The silicates are still considered innocuous when inhaled as dust, with the exception of talc, mica, and the fibrous silicates which are known as asbestos (3). The percentage of free silica in the various dusts which have been analyzed in connection with health studies of workers in dusty trades has been shown to range from 54 per cent to a trace (4). Silicosis is a chronic disease caused by the inhalation of particulate matter containing free or uncombined silica. It is characterized anatomically by generalized fibrotic changes with miliary nodulation in the lungs. Clinical signs are shortness of breath, a lowered vital capacity, a lowered capacity for work, increased susceptibility to tuberculosis, and a characteristic X-ray appearance of the lungs.

Silicosis is found to occur in such occupations as mining, the cutting of sandstone and granite, the coal industry, the smelting, refining, and grinding of metals, the manufacture of certain abrasives, the pottery industry, and the processing of the various forms of free silica. The number of workers exposed to dangerous amounts of silica dust has been estimated at more than 1 million (5).

Because of the disabling nature of silicosis (6), the extent to which exposure occurs in

industry and the number of workers involved, many surveys have been made and these investigations have resulted in the setting up of efficient protective measures in working establishments. Dust control measures, taking into consideration the chemical composition of the dust and the size of the silica particles, as well as the concentration of the dust in the air, have been instituted. There is more or less general agreement that it is desirable to avoid concentrations of more than 5 million particles per cubic foot of air in working places where the dust contains a high percentage of free silica. Granite dust, which contains about 35 per cent free silica, when in concentrations of 10 to 20 million particles per cubic foot has been found not to cause disabling silicosis in a working lifetime, while anthracite dust, containing less than 5 per cent free silica, has been found not to cause anthracosilicosis in concentrations of less than 50 million particles per cubic foot (3). Because airborne dust may differ markedly from that of the source material from which it arises, it is common practice in appraising dust hazards to determine the free silica content of samples. Furthermore, it has been indicated that toxicity increases sharply with silica dust below 3 microns in size (7). Since particles too large to be significant in silicosis production often contain a much higher percentage of free silica than fine particles of significant size, Holden and his associates (8) describe a procedure to eliminate the oversize particles before analysis.

Silicosis is occasionally found to occur under unusual or unexpected circumstances. While workers at the face in coal mines may be much less affected, silicosis has been found to be more prevalent among the mine locomotive operators in certain mines. This has been attributed to sand used as traction material. The spinning and grinding action of the wheels produces dust which, in the confined space of entries or tunnels, may rise to high atmospheric concentration. Laboratory study of substitute materials by Fairhall, Highman, and Perone (9) showed that iron ore tailings, metallurgical slags, and trap rock produce far less peritoneal reaction in guinea pigs than sand or quartz,

yet possess the requisite hardness to serve as traction material.

The mechanism and pathology of silicosis have been very adequately described. It is well recognized that very fine particulate silica is carried to the air sac or alveolus which represents the terminal dilatation of the bronchioles in the lungs. The alveoli are in intimate contact with blood vessels through which the oxygen-carbon dioxide interchange phenomena of respiration occur and they are also in contact with lymphatics which are important for the removal of foreign or irritant material. This defense mechanism is motivated by the activity of phagocytic cells which carry off the minute silica particles to the lymph nodes. There an ineffective accumulation of this material occurs and fibrotic changes take place resulting in areas which constitute the silicotic lung marking revealed by the chest roentgenogram. Just why the phagocytic cell is affected by the silica—whether, in fact, silica has a direct toxic action, or whether it initiates other effects—is still in the realm of speculation.

Certain substances, such as aluminum, iron and magnesium dusts, as well as coal and cement dusts, when used with quartz have been found to decrease the pulmonary changes associated with free silica itself. This has been attributed to a decreased solubility of the particulate silica and Denny, Robson, and Irwin (10) have shown that small quantities of metallic aluminum powder almost completely inhibit the solubility of siliceous material. While aluminum dust therapy has represented an interesting phase of the silicosis problem, it should be mentioned that Rüttner and Willy (11) have found aluminum dust itself to be fibrogenic and state that caution should be exercised in regarding it as antidotal. Furthermore, King (12) reports that, while a mixture of aluminum hydroxide with silica lowers its solubility, it does not prevent fibrosis in animals. Heffernan (13) proposed the theory that only freshly fractured quartz is biologically active and that the surface activity of the silica particles is the important factor in the production of silicosis rather than the solubility of the silicon di-

oxide. However, this theory has been vigorously criticized by Wright (14), who has attacked the various hypotheses on which this theory is based. Moreover, comparative animal experiments by Rüttner (15) have demonstrated that pure, freshly fractured quartz is no more active than "old" quartz. Vigliani *et al.* (16) have stated that measurement of the blood serum globulins can assist in both the diagnosis and the prognosis of silicosis. More recent experimental work by Baldi and Boselli (17) and by Proyard and Nizet (18) has failed to substantiate this finding. The application of the electron microscope to the examination of particulate quartz obtained from the lungs of workers has revealed a process of disintegration, according to Beintker and Meldau (19). These investigators state that the disintegration of the particle is revealed in the form of very minute droplets on the surface of the particle and that these droplets appear to be silicic acid in colloidal form. It is thought that this colloidal material may play an essential role in initiating silicosis. The more recent piezoelectric theory of fibrogenic activity of quartz has been disproved by the experimental work of Pratt and his associates (20) who found that highly piezoelectric substances other than quartz do not produce fibrosis or silicosis in guinea pigs, while tridymite and vitreous silica, both of which are not piezoelectric, do produce fibrosis.

Since free silica or quartz is the important factor in causing silicosis, the identification of this substance and its quantitative evaluation as a dust constituent are of prime consideration. The microscopic examination of such dust yields especially valuable information. Of the six distinct silica minerals, quartz, chalcedony, and opal are the more common. Tridymite and cristobalite are more or less of volcanic origin and are also found as constituents of silica bricks, while lechatellierite is exceedingly rare. Quartz and chalcedony have refractive indices near that of Canada balsam and a birefringence of about 0.009. The other silica minerals have lower indices of refraction and weaker birefringence. The microscopic examination of such industrial dusts as are known to contain free silica can only be satisfactorily



accomplished by the use of the petrographic microscope and a considerable amount of experience is necessary. Quantitative evaluation of the quartz content of a dust may be made microscopically by examining the dust and counting the dust particles in two different immersion media (21) having different indices of refraction. In one of these media all the particles are visible; in the other, having the same index of refraction as quartz, only the nonquartz particles are visible. The difference between these two estimations gives some approximation of the silica content of the dust. The method is not suitable for very fine particles and estimation based on particles of less than 10 microns in size is not good petrographic practice. Chemical methods for the estimation of free silica, such as the hydrofluosilicic acid method (22) and the fluoboric acid method (23), are tedious, time-consuming, and frequently yield information of no more quantitative value than less lengthy procedures. The X-ray diffraction method of dust analysis has become of increasing importance and is especially commendable from the point of view of speed, while it appears to yield results of as great accuracy as is obtainable by other methods of analysis. Fraser (24) has presented a method that permits for the first time an absolute procedure for the analysis of airborne solid particulates. The method makes use of the combined high efficiency of the molecular filter membrane for sampling and of the electron microscope for measurement.

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## THE SILICONES

### Characteristics

Silicon forms a large number of compounds which are analogous to those of carbon. The simplest of these is silane,  $\text{SiH}_4$ , which corresponds to methane. While these compounds have been known for some time, they were, however, of academic interest only and received no practical application until about 1940 when the unique properties of the silicones caused them to assume considerable industrial importance. The silicones,  $\text{R-SiO-R}$ , correspond to the ketones but differ from the latter in most of their properties. The methyl silicones occur as oils, resins, and elastomers or rubber-like substances. The methyl silicone oils are soluble in benzene and the lighter hydrocarbons but are only partially soluble in alcohol. Many very complex alkyl and aryl silicones have been reported and studied within recent years. Some of these substances, such as methyl silicone oil, are characterized by their chemical inertness, low temperature coefficient of viscosity, wide liquid range, and low freezing point. Their high boiling points and heat stability are important properties for many industrial applications.

### Industrial Uses

The uses of the silicones are as varied as their properties. Certain of the liquids are used as damping fluids for instruments and machinery. Other liquids find application as special lubricants for high temperature instruments, while still others are used as high viscosity heat transfer liquids and as heavy diffusion pump oils. Minute amounts prevent foaming in fuel oils—an important problem in Diesel engines—and also the foaming of aqueous solutions. The relative insolubility of methyl silicone oil in petroleum oil may account for the success of this substance in suppressing foam. Silicone greases are used as hot valve lubricants, as insulating greases for electric terminals, and in sealed bearings. Silicone rubber gaskets form air seals, oil seals, and are used as diaphragms in many new high temperature machinery applications. Silicone resins serve as

the base for high gloss, heat resistant paints; for water repellent film for coating ceramics, textiles, and paper; for high temperature varnishes for electrical insulation; and for molding rigid, laminated Fiberglas-silicone insulation forms (1, 2).

### Toxicity

As a result of a request of the Bureau of Ships, the Bureau of Medicine and Surgery of the Navy undertook a study which would show the upper limit of temperature at which rotating electrical equipment insulated by silicone could be operated with safety to the health of the workers (3). Silicone insulated electric motors were tested for periods of 96 hours continuous operation in an airtight chamber under conditions intended to simulate submarine operation. Since preliminary tests of silicone insulating materials showed what noxious substances were given off by heating, the chamber air was analyzed for oxygen, carbon dioxide, carbon monoxide, phenol, and formaldehyde. As a result, it was found that carbon monoxide was the only substance occurring in medically significant concentrations and that its concentration varied directly as the motor temperature and the duration of the test. With a motor temperature of  $200^\circ\text{C}$ ., the air carbon monoxide concentration reached 110 parts per million, which gives 12 per cent carbon monoxide hemoglobin in the blood of exposed crew members. On the basis of these calculations, as well as the state of health of exposed rats and human subjects,  $200^\circ\text{C}$ . was considered to be the maximum motor temperature compatible with health during periods of exposure as long as 96 hours at this temperature and was not productive of carbon monoxide concentrations injurious to health. New motors (motors not run at maximal temperatures to effect "curing" of the insulating material) produced the highest concentrations of carbon monoxide and this decreased in subsequent tests as the motors were cured. Insulation temperatures in excess of  $300^\circ\text{C}$ . maintained for even short periods of time constitute a hazard to health. Rowe (4), in a discussion of commercial silicones, concluded that these compounds have a low order of toxicity as a group but that



repeated skin contact with solvent compounds should be avoided. With the vapors of hexamethyl disiloxane, there is a transitory conjunctival irritation in the eye, but no corneal damage. The finished resins and rubbers are inert. Recent pharmacological studies on silicones by Gloxhuber and Hecht (5) have also indicated no toxic response to dimethylpolysiloxane oils when administered orally to rats, cats, rabbits, and dogs. Local application to the skin caused no sensitization.

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## SILVER

### Characteristics

Silver, Ag, atomic weight 107.88, density 10.5, melting point 960.5° C., boiling point 1955° C., is the most lustrous of the metals and ranks highest in thermal and electrical conductivity. It is only slightly less malleable and ductile than gold. The molten metal dissolves 20 times its volume of oxygen under pressure of 1 atmosphere and evolves this oxygen on solidification. It is soluble in nitric acid, insoluble in dilute hydrochloric and sulfuric acids, but dissolves readily in boiling sulfuric acid. The silver ion is colorless.

### Industrial Uses

During 1952, 39,419,344 ounces of silver were produced in the United States. Monetary use through the years has claimed the

largest part but this use takes the form of stock-piling and the silver is available to industry and the arts without smelter or refinery preparation. The annual consumption for war and other essential uses was estimated to exceed 110,000,000 ounces of silver, while jewelry and silverware used an estimated 20,000,000 ounces. Silver is used in solders and brazing alloys, photographic material, electrical appliances, engine bearings, military insignia, water desalination equipment, and for dental and medical supplies. Silver during the war was used in the form of heavy bus bars to conduct high amperage electric current. Silver iodide smoke is used in rainmaking.

### Toxicity

The condition known as argyria arises from the ingestion of silver salts or the inhalation of the dust of silver compounds and although the silver does not produce toxic symptoms in cases of this type, it can lead to lifelong disfigurement. Apparently the metal is deposited in the tissues in the form of insoluble salts which darken on exposure to light. While cases of argyria are thought to be rare, industrial argyria is now recognized as of increasing prevalence. Harker and Hunter (1) have reported six cases of argyria resulting from the inhalation of silver nitrate dust. Other cases of industrial exposure have arisen from the polishing and hammering of silver, silvering glass beads, the manufacture of silver fulminate, and in silver mining. In most cases, pigmentation is first noted about the eyes, appearing as a dirty gray color; it then spreads over the central portion of the face. Early pigmentation of the hands and forearms may be observed (2). Hill and Pillsbury (3) report that no systemic effects have been noted attributable to silver in either generalized or local argyria of occupational origin. However, McLaughlin and his associates (4), in a report on occupational exposure among silver finishers, found three kinds of pigment present in the lungs of one case who died following an operation; iron oxide, a fine granular pigmentation due to silver; and an iron pigment stainable with ferrocyanide. Chemical examination of this lung showed

that ash constituted 10.17 per cent of the dry weight, and of this ash, 72 per cent was iron (reckoned as  $\text{Fe}_2\text{O}_3$ ) and 6 per cent was silver (as metal). Roentgenograms of the chest were comparable with those found in electric arc welders. The X-ray changes were considered to be mostly due to iron oxide but in part to silver. Olcott and Riker (5) have recently investigated the efficacy of 2,3-dimercaptopropanol (BAL) in the treatment of experimental argyrosis. These experiments indicated that BAL is incapable of mobilizing silver which is deposited in the tissues as metallic silver or silver oxide. It therefore seems unlikely that BAL would prove of value in the treatment of argyria in man.

### Analysis

Silver may be readily separated from interfering substance by taking advantage of the insolubility of a number of its salts. Colorimetrically, small amounts of silver may be detected and determined by means of the reagents *p*-dimethylaminobenzalrhodanine (6) or diphenylthiocarbazone (dithizone). Neither of these reagents is specific for silver, however, and it is necessary to effect separation of the silver from a number of interfering metals before making the final colorimetric determination. A colorimetric procedure for the determination of as little as 0.002 milligram of silver utilizes the reaction of silver and potassium cyanonickelate carried out in a pyridine-ammonia-water system containing dimethylglyoxime (7). The most sensitive silver lines in the arc spectrum of silver are those of the following wave lengths: 3382.9, 3280.7, 2767.5, 2712.0, 2437.8, and 2413.2.

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## STRONTIUM

### Characteristics

Strontium, Sr, atomic weight 87.63, is a silver-white metal of the alkaline earth group with a specific gravity of about 2.6 at 20° C. It melts at 757° C., boils at 1384° C., is malleable, ductile and burns brilliantly in air. Strontium salts impart a red color to a flame. The metal and its compounds closely resemble calcium in both physical and chemical properties, but the strontium cation is weaker and according to Cushny (1) less toxic. Strontium forms only one ion, the divalent ion. Strontium occurs in nature as the minerals celestite ( $\text{SrSO}_4$ ), and strontianite ( $\text{SrCO}_3$ ). The metal is of some commercial importance and like the other metals of the alkaline earths it can be prepared by the electrolysis of the fused chloride.

### Industrial Uses

The production of strontium metal and its alloys in the United States in 1945 was less than in 1944 because of a recession in the wartime needs for radio and radionic tubes, in which strontium, as well as other metals, are used as "getters" for the removal of residual gases and the gases evolved during use. During the war, domestic celestite (strontium sulfate) was valuable as a substitute for barite in drilling oil wells and to some extent in the manufacture of strontium chemicals. As war demands eased, barite became more plentiful and concurrently the requirements for strontium chemicals in tracer bullets and flares were reduced drastically. Total imports of strontium minerals into the United States amounted to 14,044 short tons in 1951. In the sugar industry, the molasses containing some residual sugar is treated with a solution of strontium hydrox-



ide which forms a sparingly soluble combination, strontium saccharate,  $C_{12}H_{22}O_{11} \cdot 2SrO$ . After filtering, the saccharate is suspended in water and decomposed with carbon dioxide. The sugar is recovered from the aqueous solution by concentration and crystallization.

### Toxicity

The chemical and physiological similarity of the two elements, calcium and strontium, suggest a similarity in their metabolism in the body. A radioactive form of strontium ( $Sr^{89}$ ) is a valuable isotope for biological purposes as its half-life is 55 days, it emits 1.5 million electron-volt beta-particles, no gamma-rays, and can be produced abundantly by the cyclotron. Pecher (2) recovered 58 per cent of the dose of radioactive calcium and 33 per cent of the dose of radioactive strontium in the skeleton after 24 hours following the intravenous injection of salts of these metals into adult mice. The distribution among the different tissues was almost the same for the two elements. Both of them were concentrated in the skeleton. Uptake of calcium and strontium in the skeleton following intravenous injection was found to be nearly three times as great as that following oral administration. A higher concentration was found in the trabecular bone than in the cortical bone. This selective fixation of radiostrontium in the skeleton and the innocuousness of small doses (3) make it potentially valuable for therapeutic bone irradiation. Strontium, when ingested, is excreted mostly in the feces and when injected intravenously is found in the urine (4). When 250 milligrams of strontium were injected by vein into normal persons during 5 days, 85 to 135 milligrams were excreted during 7 days and 93 per cent of the amount excreted was found in the urine (4). Cole and his associates (5) report that strontium acetate, when injected intravenously into rats is sometimes more toxic than calcium acetate, although strontium proved to be less toxic than calcium to mice. Death usually results from respiratory failure with strontium and cardiac failure with calcium. Parathyroid extract when injected both before and also with radioactive strontium chloride resulted

in a decreased retention of radiostrontium in the femurs, a decreased fecal excretion, an increased urinary excretion, and a marked retention of radioactive strontium in the kidneys (6).

### Analysis

No very selective method for the determination of small amounts of strontium has been developed, although strontium in common with barium and calcium reacts with a number of substances, such as tannic acid and the hydroxyanthraquinones, to give a color. With sodium rhodizonate, strontium may be detected in low concentrations by the red color that this reagent produces with strontium in solution on potassium chromate test paper (7). This is said to respond to as little as 0.004 milligram of strontium in a concentration of 1:10,000. Sensitive arc lines for the spectrographic detection of strontium are 4607.34, 4215.52, and 4077.71.

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## SULFUR

### Characteristics

Sulfur exists in several allotropic modifications which differ from one another in physical properties. One form of sulfur, rhombic sulfur crystals, or  $\alpha$ -sulfur, (density 2.07 at 0° C. and melting point 112.8° C.) is nearly insoluble in water and alcohol, but dissolves in carbon disulfide. Monoclinic, or

$\beta$ -sulfur, is similarly soluble in carbon disulfide. A plastic form of sulfur prepared by pouring highly heated sulfur into water is largely insoluble in carbon disulfide. Sulfur is a poor conductor of electricity, ignites at a temperature of 363° C., and burns with a blue flame forming sulfur dioxide. It is a very active element uniting with most metals and nonmetals to form sulfides and is readily oxidized by a number of oxidizing substances to sulfur trioxide which is the anhydride of sulfuric acid. Sulfur has a valency of 2, 4, or 6, and, accordingly, forms several series of compounds.

### Industrial Uses

The production of sulfur in the United States attained a new record of 5,146,078 long tons in 1952. In order of consumption, sulfur is used by the following industries: chemical manufacturing, fertilizer and insecticides, pulp and paper, explosives, paint and varnish, dyes and coal-tar products, rubber, and food products. About three-quarters of the sulfur mined is burned and converted to sulfuric acid.

### Toxicity

The most common sulfur-containing compounds found as contaminants of industrial air are hydrogen sulfide, carbon disulfide, sulfur dioxide, and sulfur trioxide or its hydrate, hydrogen sulfate or sulfuric acid. In sulfur mining operations, apart from exposure to sulfur dioxide following explosions of hydrogen sulfide said to result from fermenting organic substances, the principal exposure to sulfur is to sulfur dust. The sulfur in itself is inert, and by far the greater portion is excreted unchanged from the intestinal tract when swallowed. The question has frequently arisen as to the effects of inhalation of sulfur dust, and reference has been made to pneumoconiosis resulting from such exposure (1). However, Pinto and his associates (2), in studying operations in which dust was formed, such as blasting and loading elemental sulfur, have not confirmed this finding. Among workers exposed to appreciable amounts of sulfur dust for a period of 7 years, no lung lesions, which could be attributed to the inhalation of sulfur dust,

were found on X-ray examination by these investigators.

### Analysis

Since sulfur may be present in a great variety of substances, such as minerals, ores, salts, gases, acids, insecticides, fungicides, and organic materials, its determination is commercially important. The determination of sulfur depends largely upon the form in which it is present and numerous chemical methods of analysis are available. For the detection of sulfur in organic material, fusion with metallic sodium or potassium is a sensitive and specific method. When the resulting sulfide is leached out and treated with solutions of sodium azide and iodine, the sulfide present catalyzes a reaction between the two with a vigorous evolution of nitrogen gas. According to Feigl (3), less than 1 microgram of sulfur may be detected by this means. The estimation of sulfur as sulfide may be made conveniently by the colorimetric nitroprusside procedure. Sodium nitroprusside yields an intense red-violet coloration with soluble sulfides in solutions slightly alkaline with ammonia and responds to as little as 1 microgram of sulfide. An excellent discussion of a variety of methods for the determination of sulfur and sulfur-bearing substances is given by Scott (4).

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## THE SULFUR CHLORIDES

### Sulfur Monochloride, Thionyl Chloride, Sulfuryl Chloride, and Sulfur Dichloride

#### Characteristics

The above chlorine compounds of sulfur are the only ones of industrial importance at



the present time. Sulfur monochloride, sometimes referred to as sulfur subchloride,  $S_2Cl_2$ , is a lemon-yellow to orange colored liquid, having a melting point of  $-80^\circ C.$ , a boiling point  $138^\circ C.$ , and a specific gravity of 1.7094. It is prepared by passing chlorine gas over molten sulfur and is purified by distillation. The vapor has a penetrating odor and is irritating on inhalation. The compound is soluble in ether, alcohol, benzene, carbon disulfide, and amyl acetate. It is decomposed on contact with water with the formation of hydrochloric acid, thiosulfuric acid ( $H_2S_2O_3$ ), and sulfur. Sulfur monochloride has the property of dissolving sulfur to such an extent that the solution consists of a thick syrupy liquid containing 66 per cent sulfur at room temperature. Advantage is taken of this property in the utilization of sulfur monochloride for the vulcanization of rubber.

Thionyl chloride,  $SOCl_2$ , is a colorless, pungent, highly refractive liquid having a boiling point of  $79^\circ C.$ , density of 1.675 at  $0^\circ C.$ , and a refractive index of 1.527. It is prepared by the interaction of phosphorus pentachloride and sodium sulfite or by the addition of sulfur trioxide to sulfur monochloride. In the latter process, a continuous current of chlorine is passed through the mixture to reconvert the liberated sulfur into chloride which then reacts with a further quantity of the trioxide. The liquid fumes on exposure to air and has an odor somewhat similar to that of sulfur dioxide. When treated with water, it decomposes into hydrochloric acid and sulfur dioxide.

Sulfuryl chloride or sulfuryl oxychloride,  $SO_2Cl_2$ , is a colorless liquid having a pungent odor and boiling at  $69.2^\circ C.$  Its melting point is  $-54.1^\circ C.$  and its specific gravity at  $20^\circ C.$  is 1.667. It is decomposed by hot water into sulfuric acid and hydrochloric acid. It is soluble in acetic acid and in benzene. It is a smoke producing substance and was used for this purpose during World War I in mixtures of certain toxic gases in order to make the toxic gas concentrations visible. Sulfuryl chloride is prepared by either heating chlorosulfonic acid in the presence of catalysts or by the interaction of sulfur dioxide and chlo-

rine in the presence of either activated charcoal or camphor.

Sulfur dichloride,  $SCl_2$ , is a reddish-brown liquid boiling at  $59^\circ C.$ , melting at  $-78^\circ C.$ , and having a specific gravity of 1.622. It decomposes at  $64^\circ C.$  and is decomposed by water. It is prepared by passing chlorine into sulfur monochloride at 6 to  $10^\circ C.$  until saturated.

### Industrial Uses

The production of sulfur monochloride during 1952 in the United States amounted to 14,198,000 pounds. Sulfur monochloride and sulfur dichloride, which react with unsaturated hydrocarbons, are used to introduce sulfur or chlorine or both into the molecule in organic syntheses. Unsaturated fatty acids are treated with these chlorides to produce cutting oil bases. These sulfur chlorides are used in metallurgy to chloridize sulfide ores and are also utilized in the manufacture of certain phenolic resins. They also find extensive use in the manufacture of dye intermediates, rubber substitutes, military gases, insecticides, and pharmaceuticals. Sulfur dichloride is used as a chlorinating agent and for this purpose may be considered the equivalent of chlorine dissolved in sulfur monochloride.

Sulfuryl chloride is used to form organic chlorides, such as chloro-derivatives of phenols or of hydrocarbons or the sulfonyl chlorides of hydrocarbons. It finds particular application in the manufacture of pharmaceuticals, dye stuffs, and rubber base plastics.

Thionyl chloride is a good chlorinating agent and is particularly useful because the products of its reactions are sulfur dioxide and hydrogen chloride, both of which are gases readily removed by heating. It reacts with organic acids to form either acid chlorides or anhydrides depending on the ratio of the acid to thionyl chloride.

### Toxicity

The vapors of the various sulfur compounds enumerated above are all primary irritants owing to the ease with which they decompose in the presence of moisture. The decomposition appears to be nearly com-

plete before the vapors reach the lower part of the respiratory tract and consequently the effects are noted principally in the upper part. The mucous membranes of the nose and throat are particularly affected and in man the irritant action on the eyes is outstanding. The pronounced irritant effect serves to some extent as a warning agent and consequently industrial injuries have been somewhat limited except in cases of accidental contact with the liquid materials. Although the toxic effects of sulfur monochloride and thionyl chloride have been amply demonstrated in animals (1), surprisingly few cases of industrial intoxication have been reported.

### Analysis

Determination of the concentration of any one of the various sulfur chlorides as an aerial contaminant should not prove difficult to the industrial hygienist, since these substances are readily hydrolyzed by water. Samples can be obtained by drawing known volumes of air through fritted glass bubbler bottles and the hydrochloric acid thus formed and neutralized may be determined by precipitation with silver chloride.

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## SULFUR DIOXIDE

### Characteristics

Sulfur dioxide,  $\text{SO}_2$ , density 2.264 (air = 1), is a colorless gas possessing a characteristic pungent and irritating odor. At  $20^\circ\text{C}$ ., sulfur dioxide may be liquefied at a pressure of about 3 atmospheres. The liquid has a density of 1.434 at  $0^\circ\text{C}$ ., a melting point of  $-73^\circ\text{C}$ ., and a boiling point of  $-10^\circ\text{C}$ .. One volume of water at  $0^\circ\text{C}$ . and 760 millimeters pressure dissolves nearly 80 volumes of gas, and the solubility at  $25^\circ\text{C}$ . and at atmospheric pressure is 32.8 volumes (1). Rapid evaporation of liquid sulfur dioxide converts it into a white solid having the melting point stated above. Sulfur dioxide does not burn

nor support combustion. Under the influence of a catalyst, it unites with oxygen to form the trioxide,  $\text{SO}_3$ . The gas is usually prepared for industrial purposes by roasting metallic sulfides, a process which is preliminary to the recovery of certain metals from their sulfide ores.

### Industrial Uses

Anhydrous sulfur dioxide liquefied under moderate pressure at room temperature is shipped in steel cylinders of 50 to 100 pounds capacity, as well as in 1-ton containers and in single unit 15-ton car tanks. It has been widely used in the liquefied state as a refrigerant and in the manufacture of sulfuric acid. In addition to these uses, sulfur dioxide is used as a fungicide and for fumigation, as well as for bleaching wool, straw, and wood pulp. It is used as a reagent in a number of organic syntheses, such as in the preparation of hydroxylamine, which in turn is used in the manufacture of dimethylglyoxime. Sulfur dioxide is also used to a certain extent in the refining of petroleum.

### Toxicity

In the melting and purifying of sulfur, the chief industrial hazard is the production of sulfur dioxide which may contaminate the atmosphere to the extent of some 6 per cent (2). Occasional exposure to sulfur dioxide also occurs in many other industrial operations and accidents with refrigerating machines have sometimes resulted in massive exposure to sulfur dioxide gas. Enormous amounts of sulfur dioxide are released in metallurgical processes and according to Hewson (3), a single plant at Trail, B. C., emitted during its operation in the years 1939 and 1940 nearly 230 tons of sulfur dioxide to the atmosphere per day. A method of reducing atmospheric pollution by varying the emission of the gas with meteorological conditions at this plant was described. As little as 0.001 per cent by volume may produce coughing, since sulfur dioxide is a primary irritant. Slightly higher concentrations may produce conjunctivitis, pharyngitis, and bronchitis. Pedley (4) found no increased incidence of respiratory disease in Canadian paper mills using the sulfite proc-



ess and examination of workers in other industries, such as smelting, was also negative. Kehoe and his associates (5) studied the effects of continued exposure to sulfur dioxide on a large group of workmen and found a significantly higher incidence of both chronic and slight nasopharyngitis and an alteration in the sense of smell and the sense of taste. The tolerable limit of sulfur dioxide is about 10 parts per million and the least detectable odor is 3 to 5 parts per million. From 400 to 500 parts per million are dangerous even for short exposure. According to Henderson and Haggard (6), the maximum concentration allowable for exposures of  $\frac{1}{2}$  to 1 hour is 50 to 100 parts per million.

### Analysis

The detection and evaluation of sulfur dioxide in air, while apparently somewhat simple, is attended by many difficulties. Most methods, such as absorption in alkali and subsequent titration with iodine, while convenient, are open to a number of objections if other aerial contaminants are present. However, for the determination of sulfur dioxide in quantity in air, the iodine titration method (7) is widely used. Sulfur dioxide may be detected even in minute amounts by its reaction with zinc nitroprusside. This reagent becomes more or less deeply red colored depending upon the amount of sulfur dioxide present (8). The test is somewhat more sensitive in the presence of a slight amount of ammonia gas. Starch-potassium iodate-potassium iodide-glycerol test paper has been adopted in England as the standard method for estimating traces of sulfur dioxide in the atmosphere (9). Concentrations down to 1 part in 250,000 can be estimated.

A resurgence of interest in the analytical determination of sulfur dioxide has followed the current agitation against air pollution and "smog", and efforts have been made to develop new methods of greater accuracy and convenience. Prominent in these investigations is that of Paulus and his associates (10). Difficulties exist not so much in laboratory procedure as in field application. The silica gel adsorption method of Stratmann (11) is of interest in this connection.

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## SULFUR FLUORIDES

### Characteristics

Sulfur hexafluoride,  $\text{SF}_6$ , is a colorless, stable gas, which melts at  $-50.8^\circ \text{C}$ ., sublimates at  $-63.8^\circ \text{C}$ ., and has a density of 5.106 (air = 1). The hexafluoride together with lower fluorides is formed when sulfur burns in fluorine. Commercially, molten sulfur is burned in a horizontal steel pipe in a stream of fluorine gas. The issuing gas consists largely of sulfur hexafluoride with some hydrogen fluoride and varying amounts of lower fluorides of sulfur, such as  $\text{S}_2\text{F}_2$ ,  $\text{SF}_4$ , and  $\text{S}_2\text{F}_{10}$ . The impurities are removed by passing the gas mixture through a nickel tube at about  $400^\circ \text{C}$ ., passing the gas in turn over copper scrap, and scrubbing with water and dilute alkali solution. The gas is finally dried over anhydrous potash or phosphorus pentoxide on glass wool and stored in steel cylinders at about 300 to 350

pounds gage pressure. In contrast with the other halogen derivatives of sulfur, the hexafluoride is chemically inert and resembles nitrogen in its stability. It is not decomposed at red heat and is only slightly affected by the temperature of the electric spark. Sulfur hexafluoride has remarkable dielectric properties which make it useful for high voltage insulation.

### Industrial Uses

The principal use of sulfur hexafluoride at the present time is largely related to its dielectric properties. It is in present use as a dielectric for electrostatic generators building up potentials as high as 5.6 million volts. It also has possible application in high voltage X-ray transformers, but for this purpose the latter will have to operate under a high pressure. The production of sulfur hexafluoride by the combustion of sulfur in fluorine gas amounted to 1,600 pounds in 1942 (1). It is possible that sulfur hexafluoride may eventually prove useful as a special refrigerant and as a stable high temperature heat transfer gas (2).

### Toxicity

Owing to its chemical inertness no toxic effect would be anticipated from the inhalation of sulfur hexafluoride. However, in the preparation of this substance variable quantities of the lower sulfur fluorides are produced, some of which are reactive chemically, corrosive in nature, and toxic. These fluorides, such as sulfur monofluoride and sulfur tetrafluoride, are hydrolyzed by water yielding hydrogen fluoride which is not only highly acid but is toxic as well. With chemically pure sulfur hexafluoride, however, in view of its chemical stability, a corresponding physiological inertness would be anticipated. This physiological inertness has been confirmed experimentally by Lester and Greenberg (3).

Sulfur pentafluoride,  $S_2F_{10}$ , is definitely toxic and was found by Greenberg and Lester (4) to cause the death of rats following a relatively short exposure of 1 hour at 10 parts per million and following 16 to 18 hours' exposure at 1 part per million. Lung injury was explained as arising from hydrolysis of the compound and the experi-

mental work indicates that sulfur pentafluoride is more toxic than phosgene.

Sulfur monofluoride,  $S_2F_2$ , kills mice within 10 to 15 minutes on exposure to a concentration of 1 per cent by volume (5).

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## SULFURIC ACID

### Characteristics

Sulfuric acid, hydrogen sulfate, oil or spirit of vitriol,  $H_2SO_4$ , is a dibasic acid obtained by the oxidation of sulfur to sulfur trioxide and its combination with water to form the commercial acid. In its very concentrated form, containing additional dissolved sulfur trioxide, it is called Nordhausen, oleum, or fuming sulfuric acid. Commercial sulfuric acid is a heavy, oily, colorless liquid with a density which increases rapidly to 1.85 for 100 per cent acid. The boiling point has no special significance since the solution loses sulfur trioxide and changes in composition until a constant boiling mixture of 98.3 per cent sulfuric acid is reached at 338° C. As a dibasic acid, sulfuric acid forms both neutral and acid salts. Two types of acid are manufactured commercially, the ordinary sulfuric acid made by the lead chamber process, and the so-called contact process acid made by the catalytic oxidation of sulfur dioxide. Sulfuric acid is highly corrosive to most metals and in addition is a strong oxidizing agent and will react with water and organic materials with the evolution of heat.

### Industrial Uses

The production of sulfuric acid in the year 1953 in the United States amounted to 14,002,534 short tons (1). The three greatest uses of sulfuric acid in that year were in



the fertilizer industry, in petroleum refining, and in the chemical and defense industries. Large amounts are also used in the iron and steel and other metallurgical industries, in paints and pigments, in industrial explosives, in rayon and cellulose film, and in the textile industry. Oleum is utilized in sulfonation processes in organic chemical manufacture and for increasing the ordinary strength of sulfuric acid to higher concentrations.

### Toxicity

Inhalation of concentrated vapor or mist from hot acid or oleum may cause rapid loss of consciousness with serious damage to lung tissue (2). Repeated inhalation of mist may cause a chronic inflammation of the upper respiratory tract and chronic bronchitis. Repeated contact with diluted solutions may cause a dermatitis. No systemic effects are noted. In cases of contact with sulfuric acid, speed in removing it is of primary importance. The immediate application of copious quantities of running water to the affected parts must be prolonged until all traces of sulfuric acid have been removed. Sulfuric acid, in concentrated form, on contact with the skin acts as a powerful caustic, destroying the epidermis, and penetrating to some distance into the skin and subcutaneous tissues, in which it causes necrosis. This causes great pain and, if much of the skin is involved, is accompanied by shock and collapse and symptoms similar to those seen in severe burns. Sulfuric acid owes its action on living tissues to its neutralization of alkalies, its dehydrating action, and to its precipitation of proteins. Most living tissue is neutral or slightly alkaline in reaction and cannot exist in an acid medium. In the pickling of metals with sulfuric acid solution, hydrogen is involved as bubbles of gas which carry a finely divided spray or mist of acid into the air. This mist is corrosive and irritating on inhalation. Furthermore, in some industrial processes sulfur trioxide is given off in clouds and has a similar but more irritating action. The fumes or mist cause an ineffective, strangling cough and irritation of the mucous membranes of the eyes and upper respiratory tract. Severe exposure may cause a chemical pneumonitis. The LD<sub>50</sub> value for sulfuric acid mist was found by Amdur *et al.*

(3) for 1½-year-old guinea pigs to be 50 milligrams per cubic meter following 8-hour exposure. For young animals the LD<sub>50</sub> value was 18 milligrams per cubic meter. According to Raule (4) the atmospheric concentration of sulfuric acid to which workers may be exposed should be less than 1 milligram per cubic meter. Erosion of the teeth due to exposure to strong inorganic acid fumes in the explosive and other industries have been recognized by the workers themselves for many years. Lynch and Bell (5) found that 45 of 126 workers engaged in the manufacture of gun cotton in which the raw materials are dipped in baths containing 70 per cent sulfuric acid, 22 per cent nitric acid, and 8 per cent water, showed erosion affecting mainly the incisor teeth.

### Analysis

The usual methods of absorption and titration or turbidimetric estimation as barium sulfate may be applied to the analysis of air for its content of sulfur trioxide or sulfuric acid mist. Benzidine forms an insoluble precipitate with sulfates which may be determined by titration in hot suspension with dilute alkali or by titration with barium chloride solution using sodium rhodizonate as indicator (6).

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### TALC

#### Characteristics

Talc, H<sub>2</sub>Mg<sub>3</sub>(SiO<sub>3</sub>)<sub>4</sub>, is a natural hydrous magnesium silicate. The foliated masses are known as talc, the compact varieties as steatite. Soapstone and potstone are impure

forms of steatite. Talc is soft, easily cut or powdered, has a greasy or soapy feeling, a high resistance to acids, alkalies, and heat, and a specific gravity ranging from 2.6 to 2.8. "Talc" is a term which, when used industrially, refers to a substance having certain physical requirements rather than to one which has a definite chemical composition. The mineral talc is a specific substance, although, as found in nature, it may be accompanied by several minerals such as serpentine (hydrous magnesium silicate), dolomite (calcium magnesium carbonate), and tremolite (calcium magnesium silicate).

### Industrial Uses

During 1952, 593,147 tons of talc, pyrophyllite, and ground soapstone were mined in the United States (1). Pyrophyllite, a hydrous aluminum silicate, is included in this figure since it resembles talc in certain physical properties and is sometimes substituted for talc. It is used as a carrier for certain insecticides, such as DDT, rotenone, pyrethrum, and nicotine. The Eastern States furnish the greater of these substances and most of the remainder comes from California and Nevada. Seven industries—paint, ceramics, rubber, roofing, paper, toilet preparations, and insecticides—absorb 79 per cent of the domestic talc.

### Toxicity

While silica itself is the classical dust producing serious pulmonary fibrosis, a type of finer fibrosis produced by silicates has also been described. However, the silicates, other than asbestos, have received little attention as possible industrial hazards. Dreessen and DallaValle in 1933 (2) reported a fine, diffuse, bilateral fibrosis of the lungs occurring in workers in a tremolite talc mill and mills producing greenish and red slate. Although these minerals had a total silicon content of about 60 per cent, most of this was in the form of silicates, for the tremolite talc contained no free silica in the form of quartz, the green slate only a trace, and the red slate 3 per cent.

In a study of workers in two talc mills and mines in northern Georgia, Dreessen and DallaValle determined that there was no

connection between talc dust exposure and the high tuberculosis mortality rate in the county (3). However, Georgia talc appears to be more injurious than tremolite talc. The dust counts were found to be high in this study, averaging as much as 1,672 million particles per cubic foot of air in the case of the packermen. The pencil cutters averaged 324 million particles per cubic foot. Only traces of free silica were found in this material. In a group of 33 men exposed to high dust concentrations, 16 had some form of pneumoconiosis. In the group exposed to low concentrations of dust, no pneumoconiosis was found. In experiments with white rats, Policard (4) found that the inhalation of talc dust for several hours daily for 12 days caused lung irritation and congestion. The lung irritation was short-lived after removal from exposure. Miller and Sayers (5), injecting dust intraperitoneally into guinea pigs, found soapstone and talc to be inert in producing tissue response. There has been some denial of the pathogenicity of such silicates in causing fibrosis and where cases of lung fibrosis have occurred these have been attributed to occasional fine particles of contaminating quartz dust (6, 7). Later investigations, however, indicate more clearly that talc fibrosis is a clinical entity. Porro, Patton, and Hobbs (8) report 15 cases of pneumoconiosis definitely attributed to talc dust and Siegel and his associates (9) describe 32 cases of advanced fibrosis in 221 tremolite talc miners. The pathology of talc pneumoconiosis, including a report of an autopsy, is described by Porro and Levine (10). In a group of 107 men who had worked with tremolite talc for 10 years or longer, Greenburg (11) found the incidence of fibrosis to be 29.9 per cent. An interesting instance of rapid development of talcosis has been reported by Alivisatos *et al.* (12) in a mill where the talc dust concentration was unusually high.

### Analysis

Talc resembles muscovite and pyrophyllite microscopically but may often be distinguished by its smaller axial angle provided an interference figure can be obtained. Birefringence is very small,  $n_v - n_a = 0.050$ .



The maximum interference colors are upper third order. Extinction is parallel to the cleavage traces in most sections. It may be necessary to make chemical or microchemical tests in order to prove the identity of talc. The analysis of dust for its talc content apart from the microscopic identification of the constituents is somewhat difficult and requires the usual type of silicate analysis applied to rocks (13) for its investigation.

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### TANTALUM

#### Characteristics

Tantalum, Ta, atomic weight 180.88, is an iron-gray metal capable of taking a good polish and is sufficiently hard to scratch glass. It has a density of 16.6 and a melting point of 2850° C. The metal is insoluble in mineral acids, including aqua regia, but is attacked by fused alkalis. Its resistance to chemical action at ordinary temperature, in

spite of its electropositive character, has made the metal important to chemical manufacturing processes in which platinum or other expensive metals had heretofore been used. The metal, although very hard, may be rolled or hammered and drawn into wire. Tantalum instruments may be cleaned in acids, sterilized and boiled in soda water. They do not rust but retain their polished surface even in a damp atmosphere.

#### Industrial Uses

Owing to its great hardness, which is equal to that of the best steel, and to its unequalled toughness and ductility, tantalum is becoming important not only to the chemical industry but in many places where these properties are especially useful. Tantalum electrolytic rectifiers are used for railways and other industrial applications. The "valve action" property of the metal makes it useful for electrolytic condensers. Tantalum has been found to be especially useful for various types of short wave and ultra high frequency radio tubes and for use in the chemical manufacture of hydrochloric acid and in the purification of bromine and phenol.

The total amount of tantalum ore imported or mined for consumption in the United States in 1951 amounted to 238,445 pounds. The metal is used in radar and other electronic tubes, neon tubes, lamp filaments, electrolytic cathodes, surgical and dental instruments, nozzles, spinnerets for synthetic textiles, electrical contacts, and temperature control apparatus, and as tantalum fluoride for a catalyst in butadiene manufacture. Tantalum oxide is a component of silica-free optical glass, having a very high refractive index and low dispersion. The carbide of tantalum is hard and is being used increasingly alone or in combination with the carbides of tungsten and titanium in steel cutting tools and dies. The increasing importance of tantalum in the chemical industry is due to its high heat transfer rate. The latter is not due to high thermal conductivity, which is about the same as steel, but to the use of extremely thin wall construction (0.013 to 0.020 inch) permitted by its unique corrosion resistance (1).

Because of its strength and corrosion resistance property and the fact that it produces no biological stimulation in contact with living tissues, tantalum is of particular use in surgery both for sutures and for skull plates (2, 3). The importance of tantalum in surgery is stressed by Olsen (4), who has also made the interesting finding that tantalum foil dressing, as well as tantalum oxide, is useful over burned areas, particularly in the case of hydrofluoric acid burns.

### Toxicity

So far no experimental work has been reported which indicates that tantalum or its compounds produce any unfavorable effects. Experimental work reported by Carney (5), in fact, shows that tantalum metal embedded in the abdominal wall and in bones of dogs caused no physiological disturbance. The use so far of tantalum in surgery has received favorable comment. Tantalum oxide dust has been shown experimentally to be nonfibrogenic (6).

### Analysis

The close chemical similarity between tantalum and columbium makes the individual identity of either of these substances somewhat difficult. A minute fragment of the oxide will give a violet to blue coloration to microcosmic salt with columbium, but tantalum oxide dissolves in the bead and imparts no color to it. On acidifying a solution of a soluble tantalate and adding tannin, a slight yellow precipitate is obtained, whereas in the case of a columbate, the colors are orange-red or a very faint blue. Tantalum and columbium can be separated by taking advantage of the marked difference between the solubilities of their double fluorides. The solubilities of the tantalum, titanium, and columbium fluorides are of the ratio 5:12:17. Schoeller's method for the separation of these metals is based upon the fractional precipitation of the oxalate solution by tannin (7).

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## TELLURIUM

### Characteristics

Tellurium, Te, atomic weight 127.61, is, in pure crystalline form, a silver-white substance with metallic luster and with more pronounced metallic properties than the other elements belonging to this group. It has a density of 6.4, a melting point of 450° C., and a boiling point of 1390° C. Although semi-metallic, it is the poorest electrical conductor of any of the metals. Like the other elements of its group, it exists in a number of allotropic modifications of which the metallic form is insoluble in carbon disulfide. Tellurium burns more readily than selenium and forms tellurium dioxide,  $\text{TeO}_2$ , which does not unite readily with water but which dissolves in alkali to form tellurites. Like the other hydrides of the sulfur group, tellurium hydride is gaseous at ordinary temperatures, has a very disagreeable odor, and is extremely toxic. Tellurium is a poor conductor of heat and its electrical conductivity, unlike that of selenium, is independent of the degree of illumination.

### Industrial Uses

The production of tellurium in the United States in 1951 amounted to 160,933 pounds, while in 1945 its production was only 80,750 pounds (1). However, producers' stocks steadily increased through the war period. Heretofore, the principal use of tellurium has been in rubber compounding, in which it is stated that tensile strengths are maintained at elevated temperatures and particularly good resistance to heat and aging



is also obtained. More recently it has attained commercial importance from its property of hardening lead which also improves the resistance of this metal to acids. Minute amounts added to cast iron increase the chill depth hardness and resistance to some acids. Although the amount of tellurium used in making a ton of chilled iron is small, the production of chilled car wheels makes the potential requirement for tellurium in the iron industry quite large (2). Tellurium is added to stainless steels to improve machineability and does not impair their corrosive resistance. Tellurium also increases the machineability of commercial bronze and is useful in alloys with tin, silver, and magnesium.

### Toxicity

Cases of tellurium poisoning were reported as early as 1920 by Shie and Deeds (3) and resulted from exposure to tellurium fumes encountered as an impurity in and around blast furnaces in a silver refinery. Seven of the 13 men examined showed evidence of tellurium absorption as indicated by garlic odor to breath and urine, suppression of sweat, dryness of the mouth, and metallic taste. Three of these had a dry, itching skin, anorexia, nausea, some vomiting, and some degree of depression or somnolence. Similar findings were reported in a much more recent case of industrial exposure to tellurium by Steinberg and his associates (4).

Keall and his associates (5) report three cases of accidental poisoning resulting from the mistaken administration of sodium tellurite for sodium iodide during retrograde pyelography. In two of these cases, death occurred after approximately 6 hours. The symptoms in order of their appearance were cyanosis, vomiting, loss of consciousness, and death. Elemental tellurium is less toxic by mouth than the soluble tellurium salts as shown by the experiments reported by De Meio (6). Rats show definite toxic effects when fed tellurium dioxide, whereas those fed elementary tellurium show practically no effects. Pathological studies indicate that tellurium is necrotizing to hepatic parenchyma and the tubular epithelium of the

kidneys. Amdur (7) has recently reported the successful treatment of three cases of tellurium poisoning with 2,3-dimercaptopropanol (BAL). Because of the restricted use of tellurium, severe cases of industrial injury due to exposure to tellurium or its compounds, apart from those noted above, have not been reported in the literature of industrial hygiene.

### Analysis

Tellurium resembles selenium in its precipitability with hydrogen sulfide. Tellurium compounds are reduced by such substances as hydrazine chloride, dextrose, tartaric acid, and sulfur dioxide. Falciola (8) claims to have detected 1 part tellurium in 500,000 parts of solution by spot testing with thiocarbamide, which forms a yellow crystalline complex which is soluble in ethyl alcohol but insoluble in other organic solvents. Pyridine has been advocated as reagent for the gravimetric determination of tellurium (9), while Hecht and John (10) obtained good results in determining 0.1 to 5.0 milligrams of tellurium by precipitation with hexamethylenetetramine. Setterlind (1942) has devised a photometric procedure for the determination of tellurium in air samples (11).

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## THALLIUM

### Characteristics

Thallium, Tl, atomic weight 204.39, density 11.85, melting point 303.5° C., boiling point 1650° C., reminds one of lead in its color, softness, high density, and low melting point. Thallium dissolves readily in nitric and sulfuric acid but not as readily in hydrochloric acid. Thallium forms two series of compounds and has valences of 1 and 3. Thallic compounds decompose, in general, upon heating, with the formation of the thallic compounds. Thallium salts color the nonluminous gas flame an emerald green and the thallium spectrum has a characteristic green line in the visible region. All thallium salts are cumulative poisons.

### Industrial Uses

Based on estimates furnished by the Fish and Wildlife Service, domestic requirements for thallium sulfate would be about 7,500 pounds for the fiscal year beginning July 1, 1946. In the United States, the metal is recovered as a by-product in the reduction of cadmium, while in Canada, it is recovered from the dusts arising from the treatment of zinc ores or scrap. Most of the metal in industry is converted to thallium sulfate, which is used as a rodenticide and for the extermination of ants and some other insects. In the optical glass industry, thallium is used for the manufacture of lenses, since the salts of thallium are characterized by their unusually high refracting power. It also has some application together with barium in the manufacture of phosphorescent

colors. However, thallium salts also have various uses in industry and in medicine, in alloys as a chemical catalyst, a fungicide, in photoelectric cells, in glass manufacturing, dye and color manufacturing, in the manufacture of fireworks, and as a depilatory.

### Toxicity

Thallium is well recognized as a very toxic substance (1, 2). The therapeutic use for children of thallium acetate as a temporary depilatory in ringworm of the scalp has repeatedly caused severe poisoning. A number of cases of suicide or murder have been reported, as well as accidental cases, many of which proved fatal (3, 4). Most of these cases resulted from ingested rodenticides or insecticides containing thallium sulfate. In acute fatal cases following ingestion of a large dose, symptoms are gastrointestinal colic, vomiting, trembling, convulsions, followed by a motor paralysis, dyspnea, and collapse (5). The production of lenses and windows from the fused halides of thallium—the technical development of which is still in the experimental stage—has recently been investigated by Sessions and Goren (6), who have made recommendations for medical and general hygienic control of exposure to thallium dust and fumes. These investigators report that thallium is not quickly eliminated from the body and therefore absorption of subtoxic amounts can build up to a toxic quantity over a period of time. It is considered to be more toxic than lead and almost as toxic as arsenic. Industrially, thallium compounds may be absorbed by inhalation of dusts and fumes, absorption through the mucous surfaces from contact with thallium in any of its physical states, and ingestion, as when individuals indulge in smoking and eating during the handling of these materials. Overexposure in industry may result in gastrointestinal symptoms, such as loss of appetite, gingivitis, stomatitis, nausea, vomiting, and diarrhea, followed by constipation. Other toxic effects frequently observed are fatigue, pain in the limbs, falling out of the hair, severe eye affection, inflammation of the kidneys, albuminuria, polyneuritis, lymphocytosis, and eosino-



philia. Dermatologic disturbances have been reported, such as erythemas and rashes. Symptoms referable to injury of the central nervous system, including restlessness, sleeplessness, excitement, and dementia, have been observed due to therapeutic overdosage. There is no known specific treatment for thallium poisoning. Sessions and Goren have made recommendations for medical and general hygienic control of exposure to thallium dust and fume (6).

### Analysis

Thallous salts resemble lead salts in many of their chemical properties, the iodide, chloride, and chromate being but sparingly soluble. The sulfide is insoluble in ammonia. Separation, both as the iodide and as the cobaltinitrite, has been used for the quantitative determination of thallium but neither is highly accurate. A new method has recently been developed for the titration of thallous salts with potassium permanganate in cold solutions in the presence of the fluoride ion (7). Small amounts of thallium may be detected by the blue color formed with benzidine in ammoniacal solution. Thallium is readily identified spectrographically, the most sensitive are lines being 5350.47, 3775.73, and 3519.21. A polarographic procedure for urinary thallium has been developed by Winn and his associates (8).

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## THORIUM

### Characteristics

Thorium, Th, atomic weight 232.12, occurs chiefly in monazite sand and in the mineral, thorite. The metal is usually obtained as a gray, amorphous or crystalline soft mass which burns readily in air to thorium oxide. In color, softness, and ductility, thorium resembles platinum. The density of thorium is 11.2 and the melting point is variously given as 1700° to 1845° C. It is insoluble in alkalis and in ordinary mineral acids but it is soluble in aqua regia. Thorium is a radioactive element which disintegrates into a series of other radioactive elements. Mesothorium, which is one of the disintegration products of thorium, is a radioactive isotope of radium and is used in luminous pigments and medicinally for its emanation product. Thorium dioxide appears to possess no acid properties even on fusion with alkalis and in this respect differs from other members of the thorium group. Thorium hydroxide is readily soluble in acids. Mixtures of thorium and certain other oxides, when heated to a high temperature, exhibit a bright luminescence.

### Industrial Uses

Although the incandescent gas mantle was more important formerly than at present, a significant amount of thorium is handled industrially at the present time, not only for the manufacture of gas mantles, but as a catalytic agent, in ceramics, in electrodes for carbon arc lights, and in certain pharmaceutical preparations. Thorium dioxide, which is a white, amorphous, insoluble powder, is used in stabilized suspension under the name of "Thorotrast" for retrograde pyelography and for roentgen visualization of the liver and spleen following intravenous administration.

### Toxicity

Thorium and its salts are only slightly poisonous. However, thorium belongs to the group of radioactive substances and several

recent references point out the danger of continued contact with thorium compounds (1-4). In the manufacture of gas mantles, a mixture of thorium and cerium nitrates in the proportion of 99 to 1 is used and from 1 to 2 per cent of sulfuric acid is invariably added, since this produces a soft, voluminous ash from six to ten times as bulky as that obtained from the pure nitrate alone. A small amount of beryllium nitrate is usually introduced, which tends to increase the hardness of the mantle. The woven material is treated with this solution, dried, and coated with collodion. In the process of preparing these mantles, workers have contracted a form of diffuse dermatitis first described in this industry by Friedländer (5). A later case also described by Friedländer presented much the same features with additional swelling of the hands and formation of deep cracks. Beyond these purely local effects, no cases of poisoning from contact with thorium compounds in industry have been reported. However, the danger of lung cancer in man following the administration of "Thorotrast" for retrograde pyelography and for roentgen visualization of the liver and spleen by intravenous administration has been referred to by Bauer (6), and carcinogenic effects of thorium following the administration of thorium compounds have been pointed out by Roussy and Guerin (7). The Journal of the American Medical Association, 1937 (8), has editorially pointed out the potential hazards of the diagnostic use of thorium dioxide. Stenstrom and Vigness (9) have shown that certain radioactive elements in the thorium series have been found in the feces, urine, and breath of two patients 6 and 7 years after the intravenous injections of "Thorotrast". Thorium-x was found in the feces and thoron in the breath in these cases. Splenitis, damage to the liver and spleen, and fibrotic changes in regional lymph nodes have also been reported following the clinical or experimental use of thorium dioxide (10, 11). It should be pointed out that in the above discussion mesothorium has not been referred to. This substance, which is extensively used in the painting of watch and clock dials, is well known to produce severe and fatal injury

(12). However, it is of interest that Evans and Goodman (13), in a recent article on the thoron content of air and its relation to lung cancer, give data for the thoron content of air in a mantle manufactory, which ranged from 23 to 400 times the recommended value of  $10^{-11}$  curies per liter of air for safe working conditions.

### Analysis

Thorium resembles the rare earths in its analytical reactions and can be separated from the common metals as oxalate or fluoride. Although a number of organic reagents react to give a color with thorium salts, none of these is specific. However, by careful separation of thorium from conflicting materials, colorimetric estimations may be made with some degree of accuracy by means of alizarin (14). New titrimetric methods for thorium have recently been described by Banks and Diehl (15). Picrolonic acid precipitates thorium quantitatively as thorium picrolonate and may be used for the gravimetric estimation of this metal. It has the disadvantage, however, of forming a colloidal solution difficult to filter. Hecht and Ehrmann (16) have shown that thorium may be more simply and rapidly determined by precipitation as  $\text{Th}(\text{C}_9\text{H}_6\text{ON})_4 \cdot \text{C}_9\text{H}_7\text{OH}$  by means of 8-hydroxyquinoline. Ryan and his associates (17) have developed a gravimetric method for the separation of thorium and uranium by means of ferron (7-iodo-8-hydroxyquinoline-5 sulfonic acid). Determination of the thoron content of air may be made by the method of Goodman and Evans (18).

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## TIN

### Characteristics

Tin, stannum, Sn, of atomic weight 118.70, melting point 231.8° C., and boiling point 2260° C., is a silver-white lustrous metal which exists in three allotropic modifications. The form of tin which is stable at ordinary atmospheric temperature consists of tetragonal crystals (density 7.29). These crystals at low temperatures pass more or less rapidly into brittle gray tin (density 5.85) and at temperatures over 170° C. they undergo transition into brittle rhombic crystals (density 6.56). Tetragonal or white tin is harder than lead but softer than gold, is very malleable, and may be rolled into thin sheets (tin foil). It is very resistant to corrosion and remains bright in moist air at ordinary temperatures. Cold dilute hydro-

chloric and sulfuric acid have very little action on tin but concentrated hydrochloric acid dissolves it readily. Tin forms two series of compounds—stannous and stannic. The tin-organic compounds are derived mainly from tetravalent tin.

### Industrial Uses

While the world production of tin reached a value of 176,000 long tons in 1939, its production in 1945 was 87,000 long tons, near the low point of this century. The consumption was seriously curtailed at the beginning of the war and a number of substitutes were necessarily devised to meet the critical situation. Forty-seven per cent of the consumption of virgin tin enters into the production of tin plate and 20 per cent into the production of solder. White-base bearing alloys, bronze, brass, and tin foil also account for the use of large quantities of tin. Our war experience indicated that tin is practically an indispensable metal. Consumption of tin in the United States amounted to 85,640 long tons in 1953.

### Toxicity

Tin is one of the least toxic of the common metals when ingested in the form of its salts. Relatively large quantities can be dissolved from acid materials preserved in tin cans without conferring any taste or flavor to food materials and without producing injury on ingestion. In an investigation made by Schwartze and Clarke, United States Department of Agriculture (1), four individuals were fed canned pumpkin over a period of 5 days during which they ingested as much as 2.75 grams of tin. The quantity of tin absorbed was small and no adverse effect was noted. The intravenous injection of stannic and stannous salts in animals indicates that the organs tolerate relatively high concentrations of tin and that the injected tin is rapidly excreted (2). The inhalation of tin oxide dust over a long period may result in the production of pseudo nodulation in the lung fields—benign nonspecific pneumoconiosis. The roentgen findings in the case presented by Pendergrass and Pryde (3) simulate those found in silicosis or barietosis. While tin is excreted to some extent

in the urine, the fecal excretion accounts for the greater part of the amount of tin salt ingested (4). Tin has been shown to exert a favorable effect on the growth of vertebrate organisms (5).

Exposure to tin tetrachloride (boiling point 114.1° C.), which occurs to some extent in industry, may cause irritation due to the caustic nature of the acid resulting from local hydrolysis. Pedley (6) investigated the possibility of injury following exposure to this substance and showed that concentrations as high as 3 milligrams per liter are well tolerated by guinea pigs and that daily exposures to this concentration produce no evidence of poisoning beyond transient irritation of the nose and eyes. On the other hand, certain organic compounds of tin, such as tin tetramethyl, have been found to produce delayed encephalopathy (7) and tin tetrahydride has been stated by Schübel (8) to be more toxic even than arsine. No industrial exposure to tin tetrahydride has been reported.

### Analysis

The determination of small amounts of tin has always been somewhat of a problem. Cacotheline (nitrobruciquinone hydrate) has been advocated for this purpose (9) but is somewhat unsatisfactory. The violet color produced is not specific for tin and many metals invalidate the test. Clark (10) has found that a number of substituted benzene-o-dithiols are specific reagents for the colorimetric determination of tin. 4-Methyl-1:2-dimercaptobenzene and 4-chloro-1:2-dimercaptobenzene are both reagents which are specific and delicate tests for tin. Sensitive arc lines for the spectrographic determination of tin are 3801.0, 3262.3, 3009.1, 2863.3, 2706.5, and 2429.5 (11).

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## TITANIUM

### Characteristics

Titanium, Ti, atomic weight 47.9, melting point 1725° C., boiling point 3000° C., and density 4.5, is a metal but in its chemical properties it shows many similarities to silicon. The reduced metal is either a gray metallic powder or a mass resembling steel. In its compact form, titanium is a hard metal with a brilliant white luster. It is brittle in the cold but can be forged at a dull red heat (1). It burns in air with extreme brilliance, burns in nitrogen at 800° C., and decomposes steam at the same temperature. When heated with carbon in an arc furnace, it forms a definite carbide. It ranks eighth among the metals in order of abundance in igneous rocks and the amount in the earth's crust is estimated at 0.43 per cent. The most important titanium ores are ilmenite,  $\text{FeTiO}_3$ , and rutile,  $\text{TiO}_2$ . Titanium forms compounds in which it has the oxidation status of +2, +3, and +4. The pure dioxide is white but natural rutile is usually brown or black. The fused oxide is difficult to dissolve but the hydrated forms dissolve readily in acids and slightly in alkalis. However, the chemistry of the titanium minerals is essentially that of an acid oxide. The oxide



fused with metal oxides or carbonates yields titanates. The properties of titanium combine the properties of stainless steel with those of strong, light aluminum alloys and are different and individualistic in comparison with those of other metals. Increasing industrial utilization will probably follow as metallurgists adapt its idiosyncrasies to specific needs. Titanium metal is prepared by the chlorination of titanium dioxide and its subsequent reduction by molten magnesium (2).

### Industrial Uses

The consumption of titanium ore in the United States in 1945 was divided between ilmenite, having an estimated  $\text{TiO}_2$  content of 381,178 short tons and rutile, with a  $\text{TiO}_2$  content of 9,144 short tons. Production of titanium concentrates in 1953 amounted to 522,514 short tons. Of the ilmenite, 98 per cent was manufactured into pigments while the remainder was used in alloys and cemented carbides. Welding rod coating consumed 80 per cent of the rutile supply and nearly all of the remainder was used in alloys and carbides. The use of titanium pigments increases at the expense of both lithopone and white lead because of its exceptionally high hiding power, its extreme whiteness, and its durability. The 1945 sales distribution pattern for titanium pigments shows that 75 per cent was used for paint, varnish, and lacquer; 10 per cent for paper; 2 per cent each for floor coverings and rubber;  $1\frac{1}{2}$  per cent each for welding rod coatings and for textiles; and 8 per cent for other uses (3). Titanium, as a deoxidizer and scavenger, is one of the best purifying agents for the production of steel and cast iron. A small amount in steel tends to reduce brittleness and increase the durability of the product. Titanium carbide is a constituent of certain cemented carbides used as cutting tools. Titanium tetrachloride was used as a screening smoke during both World Wars. In World War II, a protecting film of cold cream containing titanium dioxide was used on exposed parts of the body to prevent flash burns. The unusual dielectric properties of titanates make these compounds of interest in the electrical industry.

### Toxicity

In 1930, Carozzi (4), after reviewing the literature of titanium, concluded that because of its chemical inertia, titanium oxide is not toxic. In a study of the distribution of titanium in the organs of man, the titanium content for 17 different portions of a human body was found to range between  $1\frac{1}{2}$  and 10 micrograms per 100 grams (5). In an earlier investigation, Lehmann and Herget (6), upon feeding titanium oxide to animals for periods up to 16 months, had been unable to find any titanium in the organs. Histological study showed the organs to be normal. These investigators concluded that titanium dioxide is not absorbed by the body and that it does not exercise any toxic effect. A complete absence of toxicity was found by Verneti Blina (7) upon exposing dogs to the oxide by the respiratory, digestive, or subcutaneous routes. He also examined workmen employed in closed workshops on operations which gave off titanium oxide dust, and although the men were examined radiologically, as well as clinically, he was unable to find any appreciable lesions. Dérivé (8) describes the various salts of titanium in relation to solubility, acidity, and action on the skin. He advocates their use therapeutically for various skin conditions and for conditions affecting the teeth, such as gingivitis. It is difficult, however, to reconcile this alleged therapeutic action with the almost complete lack of physiological activity of titanium compounds in general.

### Analysis

Titanium reacts with a number of substances, either to produce a coloration or an insoluble precipitate, either of which may be used for its final evaluation. Care must be used in its separation in order to avoid loss and the separation is usually more complete in the presence of a small amount of iron. The separation of titanium from iron can be made by double precipitation of ferrous sulfide in the presence of ammoniacal tartrate. With alizarin, titanium gives a violet color; in ammoniacal solution and with chromotropic acid it gives a red-brown color. In the presence of sodium acetate, a

yellowish to red-brown color is formed with gallic acid. In neutral or slightly acid solution, titanium develops a yellow-red color with pyrocatechol and a red to reddish-yellow color with thymol (9). According to Sandell (10), the reaction with thymol for the determination of titanium is more sensitive than the hydrogen peroxide method which has long been a standard colorimetric method for this element. Sensitive arc lines for the spectrographic identification of titanium are 3998.64, 3989.76, 3372.80, 3371.36, and 3341.87.

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## TUNGSTEN

### Characteristics

Tungsten, W, atomic weight 183.92, density 19.3, boiling point 5930° C., has a melting point of 3370° C., which is higher than that of any other metal. Tungsten forms a number of oxides, of which the more important are WO<sub>2</sub> and WO<sub>3</sub>. The former (WO<sub>2</sub>) is a brown powder readily obtained by heating the canary yellow WO<sub>3</sub> to dull redness in a stream of hydrogen. By igniting this strongly in a stream of hydrogen, metallic tungsten, which is stable in air, is obtained.

The tensile strength of the drawn wire exceeds that of any other metallic substance. Tungsten form carbides, W<sub>2</sub>C and WC, when the powdered metal intimately mixed with carbon is heated in an atmosphere of hydrogen in an electric furnace.

### Industrial Uses

The consumption of tungsten ore and concentrates in the United States amounted to 14,900 short tons in 1945 as compared with 20,100 short tons in 1944. Of the total consumed in 1945, 50 per cent was converted to ferrotungsten, the form in which most of the tungsten is introduced into steel. However, 13 per cent was added directly to the steel bath in the form of tungsten concentrates. The tungsten-metal powder industry consumed the greater part of the remainder, although tungsten is also used in special tungsten alloys and in such chemicals as sodium tungstate, tungstic oxide, tungstic acid, and ammonium paratungstate. Metallic tungsten filaments are used in incandescent lamps and in radio tubes. Tungsten is an important metal in the manufacture of cemented tungsten carbide cutting tools and dies. This substance cemented in a matrix of metallic cobalt has a hardness approaching that of the diamond and, at the present time, the cemented tungsten carbide tool manufacture is one of the key industries in the United States.

### Toxicity

Exposure to tungsten in industry is related chiefly to the dust arising from crushing and milling of the two chief ores, namely, scheelite and wolframite. The preparation and use of powdered tungsten in "powder metallurgy" and the preparation of cemented tungsten carbide tool tips necessarily cause some exposure to tungsten dust. Exposure to tungstic oxide dust also occurs in the production and drying of this substance. Although very little has been published with reference to the toxicity of tungsten in general, Karantassis (1) regards tungsten as more toxic than molybdenum on the basis of ingestion and injection experiments. The feeding of 2 per cent, 5 per cent, and 10 per cent tungsten metal over a period of 70 days



has been shown to be without marked effect upon the growth of rats as measured in terms of gain in weight (2). When sodium tungstate was injected subcutaneously into 66-day-old rats after a 24-hour starvation period, the median lethal dose ( $LD_{50}$ ) was found to lie between 223 and 255 milligrams (equivalent to 140 to 160 milligrams of tungsten) (3). Ammonium paratungstate upon ingestion has been found to be much less toxic to rats than either tungstic oxide or sodium tungstate (4). Prolonged feeding experiments with metallic tungsten and a number of its compounds, recently reported by Kinard and Aull (5), indicate that the chief sites of deposition of tungsten were the bones and spleen with smaller amounts in the kidney and liver. Only traces were found in other tissues.

Recent experimental work in the Industrial Hygiene Division of the U. S. Public Health Service has failed to indicate any serious toxic effect following the inhalation or ingestion of various tungsten compounds, although heavy exposure to the dust or ingestion of large amounts of the soluble compounds produces a certain amount of morbidity and mortality. According to Lundgren and Swensson (6) intraperitoneal injection tests with animals failed to disclose any fibrogenic activity attributable to tungsten.

### Analysis

While the analytical determination of tungsten has been based on a number of organic reagents, such as benzidine, cinchonine hydrochloride, and tannic acid, none of these methods is particularly satisfactory. The thiocyanate-stannous chloride method as modified by Aull and Kinard (7) may be used to determine minute amounts of tungsten in biological materials. This method is particularly useful in the determination of atmospheric tungsten dust but it should be stressed that nickel and cobalt give color interference if present in comparable amounts. The most sensitive spectral arc lines for tungsten are 4294.62 and 4008.76.

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## URANIUM

### Characteristics

Uranium, U, atomic weight 238.7, is a hard, heavy, nickel-white metal, having a melting point of  $1850^{\circ}\text{C}$ . and a density of 18.68. It is soluble in sulfuric, hydrochloric, and nitric acids. Ordinary uranium is radioactive and isotopes with atomic weights of 234, 235, 238, and 239 are known. The isotope of weight 235 has been utilized in the so-called atomic bomb, since, when bombarded with slow neutrons, it is capable of undergoing fission with explosive violence. Uranium forms tetravalent or hexavalent compounds principally, although other valences have been reported. The uranyl salts are characterized by remarkable fluorescent phenomena. Uranium tetrafluoride is formed by the interaction of uranium trioxide and freon at  $400^{\circ}\text{C}$ . (1); uranium hexafluoride by the interaction of uranium carbide and fluorine at  $-70^{\circ}\text{C}$ .

### Industrial Uses

Previous to 1940, the demand for uranium was essentially a direct function of the use of radium. In fact, in the immediate prewar years, the expanding use of radium tended to create a surplus of uranium products. Hence-

forth, radium is likely to have a subordinate position because of the coming availability of a great number of uranium fission products and others that can furnish a large array of types and intensities of radiation (2). The common nonmilitary uses for uranium have included its application as coloring material in ceramics, as well as its use in photographic chemicals, and as a catalytic agent. Recently enormous amounts of uranium have been utilized in the manufacture of atomic bombs (3). This has also resulted in the production of a number of very useful radio isotopes.

### Toxicity

Uranium and its salts are highly toxic though no cases of serious poisoning have been reported in the scientific literature among the nearly 70,000 people employed over a period of 3 years to produce atomic bombs. In general, animals poisoned with uranium show hepatic degeneration similar to that seen with mercury poisoning which is parallel with the degree of acidosis rather than the dose (4). The chronic nephritis which occurs following the administration of uranium has been noted by a number of investigators dating from the first recorded study made by Leconte in 1853 (5). Recent studies by Holman and his associates have shown that uranium produces acute necrotizing arterial lesions affecting principally the large elastic arteries, although this specific injury is not confined to uranium (6). Although rare in man, uranium poisoning affecting four workers was reported in 1925 (7). Hoffman (8) has recently presented evidence regarding the distribution of uranium in various animal tissues and, on the basis of this distribution, regards it as an element essential for the life process. Donnelly and his associates (9) report that sodium citrate therapy given either orally or intravenously protects the kidney against uranium poisoning. The inhibition of the toxicity by alkaline solutions was recently confirmed by MacNider (10), who attributes the toxic effects of uranium to its inhibition of intracellular oxidation. Stokinger and his associates (11) found carnotite ore dust to be highly toxic to rabbits, moderately

toxic to rats and slightly toxic to a goat. The toxicity is characteristic of uranium poisoning. Uranium dioxide dust at a concentration of 80 milligrams per cubic meter and a mass-median particle diameter of 0.5 micron has been shown to be considerably more toxic when inhaled by rabbits and rats than the same concentration of uranium dioxide dust at an average mass-median particle diameter of 2.3 microns (12).

### Analysis

While uranium responds to tests with a number of organic reagents, none of these is sufficiently specific to define quantities of uranium with any great accuracy. However, the method based upon the fluorescent sodium fluoride bead test for uranium has recently been shown to be sensitive and reliable (13). Amounts of uranium as low as fractions of 1 microgram may be demonstrated by this method. The fluorescence of uranium solution under short-wave ultraviolet light has been utilized for the detection of uranium in ores (14). Furthermore, since uranium is a radioactive element, it can be detected by means of a sensitive Geiger-Mueller counter in amounts far below the usual limits of chemical detection (15). Holman and Douglas recently utilized such a method for determining the distribution of uranium in animal tissues and also the excretion of uranium following the intravenous injection of its salts (16). Currah and Beamish (17) have devised a thiocyanate colorimetric method for the estimation of small quantities of hexavalent uranium. The emission spectrum of uranium is exceptionally rich in lines although these are not particularly characteristic. Data have recently been compiled for the wave length and estimated intensities for more than 9,000 lines of the uranium spectrum (18). The detection of small amounts of uranium spectragraphically in general is difficult.

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## VANADIUM

### Characteristics

Vanadium, V, is a light gray metal, having a density of 5.9 and a melting point of 1710° C. It is soluble in nitric acid and other powerful oxidizing agents. Four oxides are known: hypovanadous oxide ( $\text{VO}$  or  $\text{V}_2\text{O}_2$ ), hypovanadic oxide ( $\text{VO}_2$  or  $\text{V}_2\text{O}_4$ ), and vanadic oxide or vanadium pentoxide ( $\text{V}_2\text{O}_5$ ). The basic properties of vanadium oxide diminish as the oxygen part of the molecule increases and the higher oxides exhibit acidic as well as basic properties. The vanadium and vanadyl cations and vanadate anions possess a variety of colors in solution varying from yellow to green, bluish-gray, blue, and violet depending on the composition of the salt.

### Industrial Uses

The increased use of vanadium in the United States is shown by the figures for production and consumption within recent years (1). The total amount of vanadium utilized in industry in 1936 was 342,720 pounds, rising to a value of 5,179,290 pounds (figure for domestic ore only) in 1943, the peak year. In 1945, the consumption fell to 3,821,000 pounds. Imports of ore, concentrates, and flue dust for that year amounted to 1,578,000 pounds. Production and consumption figures for vanadium in the United States since 1947 have not been released for security reasons. Vanadium is used for making special alloy steels and is an ingredient of the best grades of high speed steels. It exerts a degasifying and deoxidizing action which aids in forming sound steel, promotes a minimum of grain enlargement, and causes a stable solution of carbides to form in the iron matrix. These structural characteristics permit flexibility in heat-treatment, making possible the effective hardening and annealing of widely varying sections. Vanadium increases the ultimate strength elastic ratio, and resistance to shock impact and contributes to hot hard-

ness. It acts to intensify the individual properties of other major elements in steels, improves the malleability, and increases fatigue-resisting properties. Vanadium steels are used as castings, forgings, and rolled shapes; in welded assemblies, springs, airplane-propeller hubs and blades, gears, axles, high-speed tools, and armor plate, and in structural shapes (2). Apparently there is no satisfactory replacement for vanadium in the alloy steel field. Although the bulk of vanadium is used for metallurgical purposes, it has other very useful applications in industry, of which the most outstanding is that of a catalytic agent for various chemical processes. In the catalytic oxidation of sulfur dioxide to sulfur trioxide in the manufacture of contact sulfuric acid, it steadily converts 97 to 99 per cent of the material and does not suffer from poisoning as does the well-known platinum catalyst. As a catalyst also, it has other uses, for instance, in converting naphthalene into phthalic anhydride and toluene into benzaldehyde and benzoic acid.

### Toxicity

In common with many of the unusual metals, vanadium has been found as a constantly occurring substance in animal and plant tissues and has been suggested as having some physiological function (3, 4). However, Daniel and Hewston, using a spectrographic method of analysis, state that if vanadium functions in this matter it must do so in concentrations of less than 5 parts per million of organic content (5). The normal occurrence of vanadium in the blood of holothurians and ascidians suggests a possible hematopoietic function. Information regarding industrial vanadium poisoning is not extensive probably due to the large labor turnover in this industry. Exposure to dust occurs chiefly in the mining and milling of the ore, and since the bulk of our vanadium ores in the past have been imported, this dusty process has largely been confined to foreign countries. In spite of controversial statements in reference to vanadium poisoning, there is no question but that vanadium compounds are toxic, even such substances as the crude ore showing striking toxic ef-

fects on exposure to the dust. This was shown in experimental work carried out recently in the Industrial Hygiene Division, U. S. Public Health Service. Animals were exposed to patronite dust for short periods of time of  $\frac{1}{2}$  to  $\frac{3}{4}$  hour. Patronite is the ore chiefly imported into this country and consists of vanadium sulfide for the greater part. These animals showed a mortality of practically 100 per cent within 2 to 3 hours after exposure. The dust is apparently extremely irritating and causes edema of the lungs so that the animals die from drowning in their own tissue fluid. Balestra and Molfino (6, 7) have recently reported lung damage in laborers occupied in working with petroleum ash containing vanadium and point out that the general picture is different from that of ordinary pneumoconiosis. Symanski has made a careful study of 19 cases of vanadium poisoning among metallurgical employees in Germany (8). An industrial disease associated with exposure to vanadium pentoxide and described by Wyers (9) has the unusual combination of both pulmonary dust reticulation and systemic intoxication. The observed features are pallor of the skin, greenish-black discoloration of the tongue, paroxysmal cough (rarely with hemoptysis), dyspnea, pains in the chest, palpitation on exertion, tremor of the fingers and arms, barrel-shaped emphysematous chest, profuse bronchitis, bronchospasm, increased blood pressure, and reticulation on X-ray examination. Colds and pneumonia seemed to be of more frequent occurrence among these workers than in the general population. Mountain *et al.* (10) consider the toxic effects of vanadium to be associated with failure to metabolize sulfur amino acids properly. According to Mitchell (11) pH apparently plays an important role in the toxic response of mice injected with solutions of sodium metavanadate. The more acid vanadium solutions were found to be less toxic than the neutral solution. Talvitie and Wagner (12) have found the kidneys to be the major route of excretion of vanadium in the case of rats and rabbits injected intraperitoneally and intravenously with sodium metavanadate, while most of the retained vanadium was found in the bones. Mitchell



(13) has found ethylenediamine tetraacetic acid to afford a measure of protection against vanadium intoxication.

### Analysis

One of the most useful reagents for the detection of vanadium is that of tannic acid, which yields a dark-blue precipitate with vanadium and in low concentration resolves itself into a coloration. This will serve to detect vanadium in a concentration of 1 part in 10 million but care must be exercised to remove a number of interfering substances (14). An interesting specific spot test for vanadium has recently been reported by Ashburn and Reedy (15) which depends upon the reaction of slightly acid solutions with sodium tungstate. The appearance of a yellow to orange color indicates the presence of vanadium. Owing to the very large number of lines in the spectrum of vanadium, its occasional spectrographic determination is somewhat difficult. A spectrographic method for the quantitative estimation of vanadium in limited amounts of biological material (range 5 to 150 parts per million), however, has been applied by Daniel and others (16). A fused salt technique useful for the spectrochemical analysis of powdered material containing vanadium has been reported by Nachtrieb, Johnson, and Dress (17). The most sensitive group of vanadium lines in the arc spectrum are 3185.41, 3183.99, and 3183.42 Å. Talvitie's recently developed method for vanadium (18) is based on the intensity of the magenta-black color of vanadium with 8-quinolinol in chloroform solution. This method permits the determination of vanadium in the range of 1 to 50 micrograms with an average error of  $\pm 0.32$  microgram.

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## YTTRIUM

### Characteristics

Yttrium, element 39, is an iron-gray metal having an atomic weight of 88.92, density of 5.51, a melting point of 1490° C., and a boiling point of about 2500° C. It has a valence of 3 and somewhat resembles aluminum in its properties. The half-life of  $Y^{90}$  is 61 hours. Although commonly associated

with the rare earths, yttrium is not a rare-earth metal. It is found in monazite and in gadolinite. Thalenite is an yttrium silicate. Yttrium was formerly separated from these minerals by precipitation as the oxalate followed by fractional precipitation and crystallization as the double sulfate  $Y_2(SO_4)_3 \cdot 4K_2SO_4$ . However at the present time yttrium is being produced commercially by several firms by ion exchange processes (1).

### Uses

Yttrium holds some promise in the metallurgical field, in refractories and in optical glass manufacture. It is used to some extent in gas mantles and as a catalytic agent, but is chiefly of interest to and in greatest demand by the Atomic Energy Commission.

### Toxicity

Yttrium salts do not appear to be especially toxic. The  $LD_{50}$  values for rats by intraperitoneal injection were found to be 350 milligrams per kilogram for the chloride, 350 milligrams per kilogram for the nitrate and 500 milligrams per kilogram for the oxide (2). Hart *et al.* (3) found that when administered to human subjects and experimental animals in the ionized form or as a chelate of ethylenediamine tetraacetic acid, using  $Y^{90}$  as a tracer, the yttrium uptake of the tissues varied with the compound administered. Schubert and White (4) found that zirconium injected into rats an hour after the injection of yttrium caused an increase in the urinary excretion of yttrium. Later work by Dudley (5) on the metabolism of yttrium, using  $Y^{90}$  as a tracer, has shown that yttrium complexed with an excess of ethylenediamine tetraacetic acid is preferentially deposited in the bone tissue. In view of his findings on the tissue distribution of yttrium Dudley has suggested radioactive yttrium,  $Y^{90}$  as a means of delivering high energy ionizing radiation to selected tissues, particularly bone tissue.

### Analysis

The separation and determination of yttrium is difficult even when present in quantity. A chromatographic procedure is suggested for small amounts in which advantage

can be taken of the solubility relationships of the various salts. The best procedure for the detection and estimation of minute amounts of yttrium for biological experimentation is based on the use of  $Y^{90}$  as a tracer when admixture of this substance is possible. Sensitive spectral arc lines for yttrium are 4643.69, 3774.33, and 3710.30.

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## ZINC

### Characteristics

Zinc, Zn, has an atomic weight of 65.38, a density of 7.14, melting point  $419.4^\circ C$ ., and boiling point  $918^\circ C$ . It takes a white metallic luster upon polishing but the surface quickly tarnishes to the familiar blue-gray tinge. Zinc is hard and brittle at ordinary temperatures, but between  $100^\circ$  and  $150^\circ C$ . it becomes malleable enough to permit rolling and drawing. Most zinc ores contain some cadmium, the average ratio being about 200 to 1. Zinc dust is subject to spontaneous combustion in moist air, but in more compact forms does not burn readily until heated above  $500^\circ C$ . The high positive value of the oxidation-reduction-potential makes it impossible to dissolve by a number of oxidizing agents. Pure zinc is almost insoluble in very dilute acid solutions due to the large overvoltage of the hydrogen. If, however, the metal is touched with some metal with a low overvoltage for hydrogen, the zinc dissolves. It is soluble in rather concentrated alkali with the evolution of hydrogen and the formation of a zincate. Zinc oxide is amphoteric, dissolving readily in both acids and bases. Zinc hydroxide is very sparingly soluble in water ( $2.6 \times 10^{-4}$  grams



per liter), but the solubility is increased by the presence of various salts.

### Industrial Uses

In 1953, 916,105 short tons of zinc were consumed in the United States of which 406,988 tons were used in galvanizing, 178,182 tons in brass products, and 307,445 tons for zinc-base alloys. Zinc used in rolled products as ribbon and sheet zinc amounted to 20,675 tons which was 16 per cent greater than in 1952. Zinc dust is used as a reducing substance in chemical manufacturing and as a paint pigment. The principal zinc pigments, however, are zinc oxide and lithopone and its principal salts are the chloride and sulfate. Sulfuric acid made from the sulfur dioxide gases produced in roasting zinc blende (sphalerite) is an important by-product of zinc smelting. Copper and zinc salts of naphthenic acid are used as rot-proofing compounds for the treatment of fabrics and cordage.

### Toxicity

The toxicity of zinc compounds by mouth is low. The soluble salts have a harsh metallic taste and in small doses cause nausea and vomiting; larger doses cause violent vomiting and purging (1). The continued administration of zinc salts in small doses has no effects in man except those of disordered digestion and constipation. Metal fume fever or "brass founders ague" is an industrial disease which is produced on inhalation of zinc oxide fume when zinc is heated in an oxidizing atmosphere to a temperature near its boiling point as in smelting, galvanizing, in brass founding, brazing, and oxy-acetylene welding of galvanized iron (2). The symptoms are systemic, temporary, and resemble those of influenza. It is characterized by fever, chills, muscular pain, nausea, and vomiting, followed by more or less prostration. Complete recovery occurs in 24 to 48 hours. One of the characteristic features of metal fume fever is that "immunity" to these attacks is acquired by workers. However, exposure to the fumes of other zinc compounds may be more dangerous. Ten deaths and 25 cases of nonfatal injury occurred among 70 persons exposed

in a tunnel to zinc chloride fumes resulting from the burning of a smoke generator 89 yards from the entrance. The main effects were damage to the mucous membrane of the nasopharynx and respiratory tract, and a pale gray cyanosis (3).

### Analysis

The determination of minute amounts of zinc is somewhat difficult owing to the fact that zinc forms but few colored derivatives which are sufficiently specific to be applied to its evaluation. Nephelometrically, zinc may be determined as the ferrocyanide (4) or as the diethyldithiocarbamate derivative (5). Small amounts of zinc are precipitated quantitatively by 8-hydroxyquinoline (6) and by quinaldinic acid (7). Zinc in small quantities may also be efficiently separated from a number of other substances by diphenylthiocarbazone and a titrimetric method may be applied to the chloroform extract. Distinctive lines for the spectrographic recognition of zinc are 3345.0, 3302.6, 3282.3, 2800.8, 2558.0, and 2502.0.

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## ZIRCONIUM

### Characteristics

Zirconium, Zr, atomic weight 91.22, density 6.5, melting point 1860° C., boiling point > 2900° C., exists, according to the manner of preparation, in two allotropic forms. One form is a black amorphous powder and the other is usually obtained as a very hard

crystalline material resembling antimony in appearance. Very pure zirconium, which is difficult to obtain, is soft, ductile, and malleable (1). Zirconium forms only one important oxide, the dioxide,  $\text{ZrO}_2$ , an extremely hard, colorless powder with a melting point close to  $3000^\circ\text{C}$ . (almost twice that of steel). Zirconium is but slightly attacked when heated with hydrochloric, sulfuric, or nitric acids, but is rapidly oxidized by aqua regia. Hydrofluoric acid is the best solvent for this metal, as the cold dilute acid readily dissolves it. Caustic alkalies also dissolve zirconium with the evolution of hydrogen. With the exception of the dihydride and the somewhat doubtful oxide,  $\text{Zr}_2\text{O}_3$ , zirconium is quadrivalent in all its known compounds. It combines with carbon to form a carbide,  $\text{ZrC}$ , which is very hard. Zirconium metal powder under certain conditions is extremely explosive. While zirconium is not so well known as many of the common metals, it is not a rare element since it is present in the earth's crust in larger amounts than lead, copper, or zinc. The chief commercial ores are baddeleyite (zirconium dioxide) and zircon (zirconium silicate). Zirconium metal is prepared by the reduction of zirconium chloride with molten magnesium metal in a special furnace maintained at about  $900^\circ\text{C}$ . with suitable precautions to provide a neutral atmosphere during the reaction.

### Industrial Uses

The greater portion of the zirconium ore of commerce in the United States is used in the electrical and chemical porcelain field which together with the metal and alloy industry absorbed about 51 per cent of the 15,988 short tons shipped to consumers in 1945. Annual domestic requirements for zirconium minerals (1954) were estimated to be 20,000 to 30,000 tons (2). One of the valuable properties of zirconium is its great affinity for various gases, such as oxygen, nitrogen, carbon monoxide, carbon dioxide, hydrogen, and water vapor. This makes it particularly useful as a "getter" in high vacuum transmitting tubes and the pure metal powder is extensively used for this purpose (3). Copper alloys containing 5 per

cent zirconium have practically the same electrical conductivity as copper, while the tensile strength and hardness are increased by as much as 50 per cent by this addition. In steel, zirconium acts as a deoxidizer, denitrifier, and desulfurizer. Moreover, it increases the toughness and tenacity of steel. The best results are obtained when the zirconium content is equal to or less than 0.15 per cent, although in a few cases it is desirable to increase this to 0.35 per cent. Since it has an extremely high heat of combustion, zirconium powder is an efficient igniter for photoflash bulbs or as a substitute for mercury fulminate or lead azide in detonators. Zirconium finds a new use in a concentrated arc lamp which gives the nearest approach yet attained to a point source of light (4). The oxide is used as a very resistant refractory and is also an effective opacifier of fused enamels, glass, and glazes. Zircon, or zirconium silicate, is also used in the preparation of high-duty porcelain bodies, high-temperature dielectrics, enamels, and special pottery glazes. Zirconium dihydride ( $\text{ZrH}_2$ ) is used commercially in powder metallurgy for the production of sintered alloys and as an intermediate in the preparation of a master alloy of zirconium-magnesium. Furthermore, zirconium is added to magnesium for grain refinement and increased corrosion resistance (5). The Atomic Energy Commission contracts for 1956 amount to 2,000,000 pounds of zirconium distributed over a 5-year period. This metal is used in the construction of nuclear reactors because of its corrosion resistance, strength and low rate of neutron absorption. It was used in the construction of the atomic energy submarine *Nautilus* in reactor piping and various components.

### Toxicity

Zirconium has only a mild pharmacological action and may even lack physiological effect in small amounts (6). Death is caused in rabbits by the intravenous introduction of relatively large doses of zirconium as the soluble tartrate complex (150 milligrams per kilogram of body weight). The zirconium compounds in technical use are largely insoluble, however, and no occupational case



of systemic poisoning has so far been reported in man. Zirconium oxide is physiologically inert and, in fact, has been employed medicinally in roentgenography as a substitute for bismuth salts (7). Zirconium carbonate produces no acute toxic effects when administered orally or intravenously to rats in doses up to 1.5 to 2 grams per kilogram and no chronic effects in rats receiving up to 20 per cent of zirconium carbonate in their food for 17 weeks (8). However, the explosive nature of the metal powder must be kept in mind and suitable precautions observed in handling this substance.

### Analysis

The reactions of zirconium so closely resemble those of a number of other substances that its separation and determination are not simple. The analytical chemistry of zirconium has been extensively reviewed and investigated by Claassen and Visser (9). A valuable stage in the separation of zirconium is that of precipitation of the very slightly soluble zirconium phosphate,  $\text{ZrO}(\text{H}_2\text{PO}_4)_2$ , in highly acid solution. However, hafnium phosphate has similar properties and it was not discovered until 1923 that zirconium compounds frequently contained several per cent of hafnium. Separation of the two by the usual phosphate procedure is so extremely difficult that it may be accomplished only by a series of fractional precipitations. Willard and Freund (10), however, have recently developed an improved method of fractional separation based upon the rates of hydrolysis of the triethylphosphates. Alizarin may be used for the colorimetric determination of zirconium in small amounts but

requires care in its application. Fluorides, sulfates, and phosphates decrease or destroy the color while titanium, and to some extent thorium, lead to high results. For industrial analytical purposes the *p*-dimethyl-amino-phenylazobenzenearsonic acid method has been applied to the determination of zirconium in steel with good results (11). Distinctive lines useful in the spectrographic examination of material for zirconium are 3497.9, 3438.2, 3392.0, 3273.0, 2678.6, and 2571.4.

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## PART II

# CARBON COMPOUNDS

### ACETALDEHYDE

#### Characteristics

*Acetaldehyde*,  $\text{CH}_3\text{CHO}$ , molecular weight 44.05, boiling point  $20.2^\circ \text{C}$ ., melting point  $-123^\circ \text{C}$ ., density  $d_{0/4}$  0.8050, and index of refraction  $n_{18/D}$  1.3392, is a volatile, colorless liquid of marked chemical reactivity. It is miscible with water, alcohol, and ether. The production of acetaldehyde by hydration of acetylene (using mercuric sulfate as a catalyst) is an intermediate step in the manufacture of acetic acid. The acetaldehyde is oxidized with air in the presence of manganese acetate to acetic acid, and is an important modern procedure for the synthetic manufacture of the latter. It is a strong reducing agent and therefore reduces Tollen's reagent and Fehling's solution. With sodium hydroxide and iodine, it yields iodoform, which is not specific for acetaldehyde but is helpful in its identification. With phenylhydrazine, acetaldehyde yields two acetaldehyde phenylhydrazones of melting points  $98^\circ$  to  $100^\circ \text{C}$ . and  $57^\circ \text{C}$ ., respectively. Acetaldehyde yields acetaldehyde semi-carbazone when heated with semi-carbazide. This crystallizes in needles from water or alcohol and has a melting point of  $163^\circ \text{C}$ .

*Paraldehyde*. Acetaldehyde undergoes rapid polymerization under the influence of a drop of sulfuric acid or similar catalyst to a much less volatile and reactive trimer, paraldehyde. Paraldehyde,  $(\text{CH}_3\text{CHO})_3$ , boiling point  $124^\circ \text{C}$ ., melting point  $12.6^\circ \text{C}$ ., density  $d_{20/4}$  0.9943, and index of refraction  $n_{20/D}$  1.4198, is a colorless liquid less soluble in warm water than in cold. One part dissolves in eight parts of water at  $20^\circ \text{C}$ . It dissolves well in organic solvents. The polymerization of acetaldehyde to paraldehyde (in presence of traces of acid as a catalyst) reaches an equilibrium point which

at  $15^\circ \text{C}$ . contains 94.3 per cent paraldehyde and 5.7 per cent acetaldehyde.

*Metaldehyde*. A second polymer of acetaldehyde known as metaldehyde, can be obtained by the action of an acid catalyst if the temperature is carefully kept at or below  $0^\circ \text{C}$ . The melting point of this crystalline substance (in a sealed capillary tube) is  $246^\circ \text{C}$ . Metaldehyde is a tetramer but undergoes partial depolymerization when heated above  $100^\circ \text{C}$ . in the air. When pure, metaldehyde does not react with the fuchsin-aldehyde reagent nor with Fehling's solution.

#### Industrial Uses

Acetaldehyde represents an important stage in the manufacture of a number of synthetic chemicals. In many of these operations it appears only as an intermediate. Apart from this important use in industry, acetaldehyde has some application as a solvent and is also used in medicine as an inhalant in catarrh and ozena.

Paraldehyde is used as a diluent in the manufacture of pigments and varnish and as a latent solvent for nitrocellulose acetate. It has some medicinal use as a sedative and an antispasmodic and is frequently used when other hypnotics are contraindicated.

Metaldehyde received extensive use during the war as a fuel for heating combat rations. For this purpose, it was compressed into round, white tablets about 1 inch in diameter and about  $\frac{1}{4}$  inch thick. They superseded the former wax fuel tablets and canned solidified alcohol.

#### Toxicity

In the view of the equilibrium relationships of acetaldehyde and its polymers and the relative ease of reconversion of the polymers to acetaldehyde, no attempt has been made to differentiate the toxicities of these substances. Apparently the toxic effects of paraldehyde are essentially those of acetal-



dehyde. In general, acetaldehyde is an irritant to mucous surfaces and at the same time has a general narcotic action on the central nervous system. The low concentrations which usually are found in practice cause irritation of the eyes, nose, and upper respiratory passages, as well as bronchial catarrh. In chronic intoxication, the symptoms resemble those of chronic alcoholism, such as loss of weight, anemia, delirium, hallucinations of sight and hearing, loss of intelligence, and psychic disturbances (1). Higher concentrations cause headache, stupefaction, bronchitis, pulmonary edema, diarrhea, albuminuria, fatty degeneration of the liver and of the cardiac muscles, and death. While it has been stated that individual cases have survived large doses of paraldehyde, in a recent case, death of a child occurred following the administration of 3 grams of metaldehyde (2). Death from large doses results from respiratory paralysis. With lethal doses, pulse and respiration become progressively slower, followed by complete respiratory paralysis, the heart continuing to beat 5 minutes after respiration has ceased (3). The postmortem examination of tissues has shown swelling and redness of mucous membrane, fatty degeneration of the liver and kidneys, and areas of acute degeneration of the neural cells of the brain (3, 4). Stotz, Westerfeld, and Berg (5) have shown that while acetaldehyde is quite toxic at higher levels it is rapidly metabolized. Hitchcock and Nelson (6) studied the metabolism of acetaldehyde and paraldehyde in mice and found that acetaldehyde is destroyed four times as rapidly as paraldehyde and that much smaller quantities of acetaldehyde are excreted in the expired air than of paraldehyde. Handovsky (7) found that the intravenous administration of small amounts of acetaldehyde in anesthetized dogs caused a sharp rise in blood pressure and a cardiac acceleration. Maximum allowable concentration values for acetaldehyde lie within the range of 50 to 200 parts per million.

### Analysis

Acetaldehyde vapor may be absorbed in aldehyde-free alcohol in a sintered glass

bubbler, or air samples may be taken in vacuum bulbs. The estimation may be made by one of several colorimetric methods or by a suitable volumetric method. As an example of the latter, acetaldehyde may be absorbed in water and advantage taken of the sulfite-binding property of aldehyde in general to react with sodium bisulfite, the uncombined bisulfite being titrated with iodine. When treated with Schiff's reagent (a solution of fuchsin decolorized by sulfurous acid), most aldehydes produce the violet-red color of fuchsin in proportion to the amount of aldehyde introduced. This method may be applied to acetaldehyde providing the reagents used are aldehyde-free. Acetaldehyde also gives yellow to brown colors with benzidine hydrochloride (8) and *m*-phenylenediamine hydrochloride (9) which, although not wholly specific for acetaldehyde, are useful for its colorimetric determination. A method for the colorimetric determination of acetaldehyde in blood, which could well be adapted to the determination of acetaldehyde as an aerial contaminant, has also been recently developed by Stotz (10). This method is based on the depth of coloration produced with *p*-hydroxybiphenyl reagent. Paraldehyde and acetaldehyde weight for weight were found to yield equal color intensities. Hitchcock and Nelson (6) determine paraldehyde in the tissues and in expired air by depolymerization of the paraldehyde to acetaldehyde in hot dilute sulfuric acid and the absorption of the liberated acetaldehyde in sodium bisulfite solution, followed by iodimetric titration.

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## ACETIC ACID

### Characteristics

Acetic acid, ethanoic acid,  $\text{CH}_3\text{COOH}$ , boiling point  $118.2^\circ\text{C}$ ., melting point  $16.635^\circ\text{C}$ ., density  $d_{20/4}$  1.04926, index of refraction  $n_{20/D}$  1.36976, and vapor pressure 11.4 millimeters of mercury at  $20^\circ\text{C}$ ., is a clear, colorless liquid at ordinary temperatures and is miscible with water at all concentrations. The so-called glacial acetic acid is 99.5 per cent acetic acid. It has a sharp characteristic odor, is volatile with steam, and its neutral salts are nearly all soluble in water. When treated with phosphorus pentachloride acetic acid gives acetyl chloride having a boiling point of  $51^\circ\text{C}$ . Acetic acid does not reduce potassium permanganate, in which it differs from formic acid. Ordinary vinegar prepared by fermentation is 6 per cent acetic acid. The preparation of pure acetic acid from crude vinegars is not practical and the chief source of the concentrated acid was formerly pyroligneous acid, resulting from the destructive distillation of wood. Pure acetic acid is now prepared by synthetic processes which start with propane gas or calcium carbide, by the oxidation of ethanol in the presence of a metal catalyst, or the hydration of acetylene and oxidation of the resulting acetaldehyde. Peracetic acid,  $\text{CH}_3\text{COOOH}$ , is now manufactured in commercial amounts in the form of a stable 40 per cent solution containing 8.6 per cent active oxygen.

### Industrial Uses

The production of synthetic acetic acid in the United States in 1954 was 442,007,000 pounds; of so-called natural acetic acid over

19,022,000 pounds (1). The principle uses for commercial acetic acid are for the manufacture of plastics and resins, manufacture of acetic anhydride and organic acetates or esters, and for textile processing. Minor uses include the manufacture of metallic acetates, drugs and pharmaceuticals, paint and pigments, and photography and rubber chemicals.

### Toxicity

The vapor of acetic acid is sharp and penetrating, causing lacrimation and irritation of the mucous membranes in general. While acetic acid is frequently regarded as more or less harmless, perhaps owing to its association in dilute form with vinegar, the pure acid is dangerous in contact with the skin, causing painful burns which are slow in healing. Sklodowski (2) discusses 21 cases of poisoning from the ingestion of strong acetic acid, including three deaths. Hemoglobinuria was a characteristic finding in most of these cases. Woodard and his associates (3) have measured the  $\text{LD}_{50}$  dosage by mouth for acetic, dichloroacetic ( $\text{CHCl}_2\text{COOH}$ ), and trichloroacetic ( $\text{CCl}_3\text{COOH}$ ) acids and have found that these are of the same order of magnitude (the  $\text{LD}_{50}$  dose of acetic acid for rats was 3.31 grams per kilogram of body weight), while the toxicity of monochloroacetic acid ( $\text{CH}_2\text{ClCOOH}$ ) for mice is approximately 25 times and for rats approximately 40 times those of the other three acids. In sufficiently dilute form, acetic acid is not toxic nor are the acetates, such as potassium and sodium acetate, in dilute solution. However, Hemingway and Sparrow (4) have shown that acetic acid in concentrations of 30 millimols per kilogram and sodium acetate in concentrations of 70 to 80 millimols per kilogram is the maximum tolerated dose for rats over a period of 2 weeks. The toxicity of the latter is very low even on intravenous injection. Concentrations up to 0.25 per cent have been shown to produce no effect on the growth, appetite, or consumption of fluid when given as the sole drink to rats (5). However, Parmeggiani and Sassi (6) have found evidence of blackened skin, hyperemic conjunctiva, and congested pharynx in em-



ployees exposed for periods up to 12 years to a working atmosphere of 26 to 76 parts per million of acetic acid. A number of agencies have adopted a maximum allowable concentration value for acetic acid vapor of 10 parts per million.

### Analysis

The analytical determination of acetic acid as a contaminant presents no particular difficulty when present as a single constituent. Measured volumes of air may be drawn through a sintered glass bubbler containing a measured amount of standard alkali solution and the excess alkali may then be back-titrated. Where other acids are present, it may be necessary to trap the acetic acid in alkali and separate it by distillation with phosphoric acid.

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## ACETIC ANHYDRIDE

### Characteristics

Acetic anhydride,  $(\text{CH}_3\text{CO})_2\text{O}$ , is a colorless liquid with a sharp, irritating odor. It is characterized by the following physical properties: boiling point  $140.0^\circ\text{C}$ ., melting point  $-73.1^\circ\text{C}$ ., density  $d_{20/4}$  1.08112, and index of refraction  $n_{20/D}$  1.3904. It is soluble in cold water to the extent of 12 per cent and is slowly hydrolyzed to acetic acid. The vapor pressure of acetic anhydride at  $20^\circ\text{C}$ . is 4 millimeters of mercury, while at  $100^\circ\text{C}$ . it is 210 millimeters of mercury. It is a readily combustible liquid and introduces a potential fire hazard when it is

stored or handled. The lower and upper limits of inflammability of acetic anhydride in air as determined by the Bureau of Mines are 2.67 and 10.13 per cent by volume. Minimum ignition temperatures in air and oxygen, respectively, are  $392^\circ\text{C}$ . and  $361^\circ\text{C}$ . At elevated temperatures, an irritating vapor is given off which when mixed with air is explosive within the limits of 2.7 to 10.1 per cent by volume of air. Acetic anhydride is prepared industrially by passing the vapor of glacial acetic acid over a catalyst (sodium ammonium phosphate and boron phosphate) at  $600^\circ$  to  $620^\circ\text{C}$ . The standard method of preparation consists in treating sodium acetate with sulfur chloride ( $\text{SCl}_2$ ) and chlorine. Acetic anhydride, sodium chloride, and sodium sulfate are formed. Acetic anhydride is also prepared synthetically on a commercial basis from ethylidene diacetate. The latter is made by passing acetylene into a suspension of mercurous sulfate in concentrated or glacial acetic acid. On distillation of ethylidene diacetate in the presence of a small quantity of anhydrous salts, such as sodium pyrophosphate or zinc chloride, the ethylidene diacetate decomposes into acetic anhydride and acetaldehyde which are readily separated by fractionation. Another industrial process for the manufacture of acetic anhydride utilizes the highly unsaturated and reactive substance ketene,  $\text{CH}_2=\text{C}=\text{O}$ , which can be prepared efficiently by cracking acetone. Ketene reacts readily with acetic acid to form acetic anhydride.

### Industrial Uses

During 1954, 690,643,000 pounds of acetic anhydride were produced in the United States. Approximately two-thirds of this amount was used in the manufacture of synthetic fibres, while the manufacture of plastics and resins ranks second. Acetic anhydride is used in the manufacture of acetylsalicylic acid (aspirin) and other pharmaceuticals, and also in the manufacture of perfumes and flavors, and in textile dyeing.

### Toxicity

Acetic anhydride, in either the liquid or vapor form, has an irritant and corrosive

action on the mucous surfaces. Its irritant action is generally assumed to be due to the hydrolytic product (acetic acid) formed as a result of interaction of the anhydride with moisture in the tissue. While acetic anhydride forms acetic acid in contact with water, this does not occur with any great rapidity and it is still a moot point as to whether there is any systemic poisoning due to acetic anhydride alone, or whether the entire toxic effect is due to liberated acetic acid. Lehmann and his associates (2) found that man is generally more sensitive to the effects of inhalation of acetic vapor than animals. The effects of exposure were so marked that workmen could not endure an atmosphere of 800 parts per million for longer than 3 minutes. Acetic anhydride is a marked lacrimator and due to its warning properties, generalized systemic effects are not likely to occur. The symptoms are coughing and a burning sensation in the nose and throat. Dermatitis and chronic eye irritation may result from repeated or prolonged contact with acetic anhydride.

### Analysis

The determination of the amount of acetic anhydride present as an aerial contaminant may be made by bubbling a measured volume of air through a fritted glass bubbling apparatus containing a known amount of alkali, followed by back-titration with a standard acid solution. Acetic anhydride when mixed with a few drops of aniline and boiled, forms acetanilide (boiling point 114° C.). Aceto-*p*-toluidide (melting point 148° C.) is similarly formed when *p*-toluidine is used in place of aniline. Diggle and Gage (3) determine acetic anhydride in air by absorption in alkaline hydrazine, treatment with ferric chloride, and photoelectric measurement of the ferric acetohydroxamic acid complex.

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## ACETONE

### Characteristics

Acetone, dimethylketone, 2-propanone,  $\beta$ -ketopropane, pyroacetic ether,  $\text{CH}_3\text{COCH}_3$ , boiling point 56° C., melting point -94° C., density  $d_{20/4}$  0.7912, index of refraction  $n_{20/D}$  1.3590, is a colorless, clear, volatile, highly inflammable liquid, miscible with alcohols, ethers, halogenated hydrocarbons, and water, and having a characteristic ethereal odor and a pungent, sweetish taste. Since the flash point is -20° C., the danger of fire and explosion must be considered when used industrially. Acetone is an excellent solvent for many carbon compounds and for many inorganic salts. Acetone dissolves acetylene rather freely and this property is usefully employed in the commercial handling of acetylene. The latter, when compressed alone under pressures above 2 atmospheres, tends to decompose explosively. When dissolved in acetone, however, it may be compressed to 10 or 15 atmospheres with safety. On boiling with benzaldehyde and a concentrated solution of barium hydroxide in dilute alcohol, acetone yields dibenzalacetone (melting point 111° C.). With iodine and sodium hydroxide in the cold, it yields iodoform (melting point 119° C.). A dilute solution in water gives a red color with alkaline nitroprusside which changes in tint on adding acetic acid. With saturated aqueous sodium bisulfite, acetone yields a sulfite addition compound. Acetone oxime and acetone phenylhydrazone are not recommended as derivatives for identification. While formerly prepared by the dry distillation of calcium acetate or from crude wood spirit, it has been more recently obtained on a technical scale by the fermentation of starch and sugar-containing materials by such bacteria as *B. macerans* and *B. acetoethylicum*. During the war period, production from the oxidation of isopropyl alcohol greatly exceeded that of the fermentation process, approximately six times as much being obtained by the oxidation proc-



ess as by fermentation. Normal blood contains about 1 milligram per 100 grams of blood of the so-called ketone bodies (acetone, acetoacetic acid, and  $\beta$ -hydroxybutyric acid). The concentration of acetone is markedly increased in fasting individuals, in toxemias of pregnancy, in persistent vomiting, and in diabetes. In severe diabetes, values of 300 milligrams per 100 grams of blood have been recorded.

### Industrial Uses

The production of acetone by fermentation in the United States during 1954 amounted to 20,866,000 pounds, while production from isopropyl alcohol amounted to 403,681,000 pounds. Chemical manufacture accounted for the use of the bulk (42 per cent) of wartime acetone; 15 per cent was used as solvent, 11 per cent for coated fabrics and rayon, 6 per cent for drugs and pharmaceuticals, and 5 per cent for resins and plastics. Acetone is used as an absorbent for acetylene stored in cylinders, in the manufacture of rubber, of varnish, lacquer, and other protective coatings, as a denaturant for industrial alcohol, in photography, and as the raw material for synthetic manufacture of numerous substances, such as chloroform, iodoform, and diacetone.

### Toxicity

In general, the effect of acetone is similar to that of ethyl alcohol, although its narcotic effect is somewhat greater. Following inhalation, elimination occurs chiefly through the respiratory tract and the kidneys with rather rapid elimination of the material absorbed. Elimination of the absorbed residual acetone occurs for more slowly. The local irritant effect is not strong but is noticeable on mucous membranes. Exposure to heavy concentrations produces narcotic symptoms, bronchial catarrh, and headaches with the feeling of oppression. It should be pointed out that pure acetone is less toxic than the impure trade products. As the duration of exposure increases, there is a gradual fall of rectal temperature, respiratory rate, and pulse. The rate of this change is roughly proportional to the concentration of acetone vapor (1, 2). Absorp-

tion of acetone by workers exposed to acetone vapor has been definitely demonstrated by finding this substance in the urine of individuals so exposed (3). While the toxic effect of acetone is not great, it is necessary to observe precautions in its use in industry, both from extensive inhalation and, because of its high volatility, from explosion and fires. There is no evidence of chronic effects in man following continued exposure to low concentrations of acetone (4). The lowest concentration of acetone which would apparently produce mild intoxication and, hence, possibly constitute an industrial hazard is 5 milligrams per liter (2,110 parts per million) (4). Exposure to high concentrations causes restlessness and vomiting in man, followed by progressive collapse with stupor and periodic breathing (5). The injurious effects of high concentrations of acetone vapor on the eye have been ascribed to pure acetone itself rather than to impurities (6). In animals Dervillee *et al.* (7) found that guinea pigs survived for 2½ hours at a concentration of acetone vapor of 0.592 gram per liter and rabbits for 1½ hours. With lower concentrations, or shorter exposure, death occurred only after repeated exposure.

### Analysis

The determination of acetone in air samples may be conveniently carried out by the absorption of the substance in water through which the air is slowly bubbled. Several methods are available for determining the acetone content of this aqueous solution, such as development of a red color with sodium nitroprusside, or the formation of a reddish-brown color with aniline in alkaline solution. A variation of the iodoform reaction for acetone has been applied to its quantitative determination by Goodwin (8). More recently, however, a micromethod for the determination of acetone in air has been developed by Greenberg and Lester (9) which depends upon the reaction between acetone and 2,4-dinitrophenylhydrazine to form the corresponding hydrazone. The latter is separated by extraction with carbon tetrachloride and colorimetrically deter-

mined. This method is stated to be particularly rapid and accurate.

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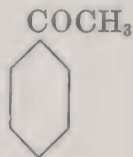
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### ACETOPHENONE

#### Characteristics

Acetophenone, phenylmethyl ketone, acetylbenzene



occurs commercially either as crystalline leaflets melting at 20.5° C., or as a colorless liquid. Its boiling point is 202° C. per 750 millimeters of mercury, or 94.5° C. per 20 millimeters. It is readily soluble in alcohol, ether, benzene, and chloroform, but is only slightly soluble in water. It dissolves in concentrated sulfuric acid with an orange color.

Acetophenone has a density of  $D_{15/15}$  1.0329 and index of refraction of  $n_{19/D}$  1.53418. Commercially it is prepared from benzene and acetyl chloride, or from benzaldehyde and diazomethane, or catalytically from acetic and benzoic acids. It has typical ketonic properties, forming a characteristic oxime having a melting point of 60° C. and phenylhydrazone (melting point 105° C.). It does not combine, however, with sodium sulfite. Nascent hydrogen converts it readily into phenylmethyl carbinol, while oxidation with potassium permanganate converts it to phenylglyoxylic acid. Acetophenone occurs to a small extent in coal tar and, having feebly basic properties, is extracted from the heavy oil fraction with sulfuric acid. It is somewhat widely used in organic syntheses, as a solvent for cellulose ethers and esters, and in perfumery. It has a persistent odor reminiscent of orange blossoms and jasmine.

#### Toxicity

Acetophenone has pronounced narcotic properties and was originally proposed as an hypnotic by Dujardin-Beaumetz and Bardet (1) under the name "hypnone". However its uncertain and toxic qualities have curtailed its use as a somnifacient. There is no question but that acetophenone, when administered either subcutaneously, intravenously, or by mouth, produces complete anesthesia and analgesia in animals. Frequently however the animals pass into deep coma and death. With sublethal doses the narcotic action is uncertain. The older literature states that acetophenone is changed to benzoic acid and excreted as hippuric acid and also conjugated with glucuronic acid. Thierfelder and Klenk (2) found that intraperitoneally administered acetophenone is excreted to the extent of 91.7 per cent as hippuric acid together with a small amount of mandelic acid and some  $\alpha$ -phenylethyl alcohol. The benzene ring is apparently left intact. On applying their range finding test, Smyth and Carpenter (3) found the single dose oral toxicity to rats of acetophenone to be 3 grams per kilogram of body weight. No industrial systemic poisoning has been reported from exposure to acetophenone, probably because of its low vapor pressure at



room temperature. However, dermatitis has followed skin contact with this substance and Katz (4) reports acetophenone as a skin irritant.

### Analysis

Acetophenone may be detected by the deep red color formed with alkaline salicylaldehyde (5), or microchemically by condensation with either *p*-nitrophenylhydrazine (6), or *p*-bromobenzohydrazide (7). Very small quantities may be determined satisfactorily by precipitation with 2,4-dinitrophenylhydrazine (8).

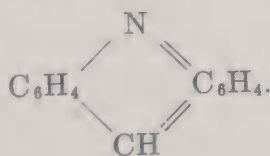
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## ACRIDINE

### Characteristics

Acridine is a heterocyclic compound chemically related to anthracene. It is a basic constituent of the heavy tar oils produced in the high temperature carbonization of coal and has the formula



Acridine occurs in the crude anthracene fraction separated from coal tar. It may be prepared synthetically from diphenylamine and either chloroform or formic acid when heated with zinc chloride at 200° C. It may also be prepared by passing benzyl aniline through a red hot tube. Acridine forms colorless, needle-like crystals which sublime at 100° C. and melt at 110° C. Acridine boils at 345° C. It is sparingly soluble in hot water but is soluble in alcohol, ether, or carbon disulfide. The substance has a characteristic, pungent odor and a burning, acrid taste. The solution of acridine has a strong, blue fluorescence which also characterizes many acridine derivatives. It reacts with strong mineral acids to give yellow, well-crystallized salts which are partially hydrolyzed with hot water. Acridine is the parent substance for a series of dyes, such as acridine orange NO, acridine yellow, trypanflavine, and chrysaniline.

### Industrial Uses

The acridine dyes are not usually prepared from acridine itself, as the preparation of the latter is somewhat difficult. Benzoflavine, for instance, is synthesized from benzaldehyde and *m*-toluylene diamine. This dye is extensively used in calico printing. Acridine orange occurs in commerce as the zinc salt and gives a fluorescent color on cotton or silk. Certain dyes derived from acridine, such as acriflavine and proflavine, are used as antiseptics and other derivatives are used in chemotherapy. Atebrin (quinacrine hydrochloride), for instance, is used in the treatment of malaria (1); rivanol (2-ethoxy-6,9-diaminoacridine), a yellow crystalline substance, is used in the treatment of streptococcal infections.

### Toxicity

Acridine is an irritant to the skin and mucous membranes. Its dust and vapor are powerfully sternutatory. The burning and itching of the skin on contact with acridine is followed by inflammation and in severe cases the respiration rate and blood pressure are increased. White (2) lists a number of acridine derivatives as sensitizers to sunlight, but states that in spite of its strongly

irritant skin action, it does not give rise to cancer. Doubtless the irritant skin effect of acridine serves as a warning action and accounts for the fact that no serious industrial poisoning has so far been reported. However, the possibility of such industrial poisoning should not be minimized. Leopoldsberger (3) has pointed out that porous coal bricks may contain acridine in slightly volatile form. At high temperatures and during sun exposure, damage to the cornea, skin, and mucous membranes may occur following the liberation of acridine vapor. Rubbo (4) determined the LD<sub>50</sub> for mice of 65 acridine derivatives and found that their toxic and antibacterial action was correlated with their ionization as bases. Powdered acridine derivatives, when applied to guinea pig muscle, were found to be locally toxic and this was not dependent on their ionization. In a recent study of the health of workers engaged in the manufacture of rim steel (5), it was found that acridine vapor was given off in abundance from the tar coating of the molds during the pouring of the molten metal. The vapor proved very irritating on inhalation. No maximum allowable concentration value for acridine vapor has so far been established in industry.

### Analysis

No analytical method has been developed for the estimation of acridine vapor or dust as an aerial contaminant. However, the reactivity of acridine is marked and could well be usefully employed in the development of a colorimetric method. In addition to the strong fluorescence of its derivatives, acridine as the hydrochloride forms a series of colored complexes with various metals, such as iron (red), cobalt (green), and zinc (yellow) with ammonium thiocyanate. Since acridine forms an addition compound with sodium acid sulfite, it is possible that this reaction can also be usefully applied to the determination of traces.

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## ACROLEIN

### Characteristics

Acrolein, propenal, acrylaldehyde, acrylic aldehyde,  $\text{CH}_2=\text{CH}-\text{CHO}$ , boiling point 52.4° C., melting point -87.7° C., density  $d_{20/4}$  0.841, index of refraction  $n_{20/D}$  1.39975, is a colorless, inflammable liquid with a very pungent odor. It is unstable and polymerizes to disacryl, which is a white solid insoluble in water, acids, or alkali. This polymerization occurs even with the pure substance and is favored by light, heat, and certain impurities. In the presence of inhibitors (such as traces of polyhydric phenols), acrolein is stable almost indefinitely. In the presence of sodium hydroxide solution, acrolein polymerizes to a white, fluffy powder. With phenylhydrazine, it yields phenylpyrazoline, crystallizing as yellowish tablets from hot ligroin, and having a melting point of 50 to 51° C.

### Industrial Uses

Acrolein is principally used in organic synthetic processes, such as the manufacture of synthetic perfumes (in combination with various butadiene derivatives) and in the manufacture of allyl alcohol. It forms condensation products with phenol and with urea, which constitute certain commercial plastics. Condensation products of amines and acrolein are strong accelerators of vulcanization. Acrolein was used by the French in World War I as a toxic lacrimator but was not very successful because of its chemical instability (1). It is employed as a reagent in making colloidal preparations and as a warning agent (2) in refrigerators using methyl chloride.



## Toxicity

Acrolein is an irritant and even in low concentrations affects the upper respiratory tract. On inhalation of high concentrations, it causes edema of the lungs. It causes intense irritation of the eyes and nose following short exposure. Acrolein commonly occurs when fats and oils are heated to high temperatures and it is the principal irritant in the exhaust gas from internal combustion engines. Since it is formed from glycerol by dehydration, it is found as an atmospheric contaminant in several industries in which this substance is employed. Kamen (3) has drawn attention to the possible association of acrolein and shock associated with burns. Acrolein injected into experimental animals subcutaneously, intraperitoneally, or intravenously produces a condition identical in its clinical and pathological manifestations to that generally accepted as "shock". Henderson and Haggard (4) state that 1 part per million of acrolein in air is immediately detectable, that 5.5 parts causes intense irritation, and that 10 parts per million is lethal in a short time.

## Analysis

The detection of acrolein is somewhat complicated by the similar reactions of other aldehydes. Most distinctive is a variation of the usual fuchsin-aldehyde test. Certified *basic* fuchsin (0.2 gram) is dissolved in 10 milliliters of freshly prepared cold, saturated, aqueous solution of sulfur dioxide. It is allowed to stand until colorless and then diluted to 200 milliliters. To 5 milliliters of this reagent, 2 milliliters of the aqueous solution of acrolein is added, stoppered, and allowed to stand overnight. The solution will then be colored a deep violet-blue. Add an equal volume of concentrated hydrochloric acid. The color successively changes through yellow-green and blue-green to violet-blue. Acrolein is distinguished from all other common volatile aldehydes by these collective color changes. Berezova has discussed in detail three colorimetric methods useful for the determination of acrolein in the air of industrial plants (5). Circle and his associates

have utilized the color developed with tryptophane for the determination of acrolein (6). Other aldehydes interfere at an acrolein concentration of 25 micrograms and therefore must be at a relatively much lower concentration than that of acrolein for satisfactory results. Korenman has devised a micromethod based upon the formation of iodoform with iodine, the excess of which is back-titrated (7). Where the air contaminant is known to be acrolein, it may be conveniently evaluated by means of a permanganate titration. Standard potassium permanganate solution is added in excess to a measured amount of the sample secured by bubbling a known volume of air through water in a sintered glass bubbler. Sulfuric acid is added and the solution is heated for 15 to 20 minutes on a water bath, an excess of standard oxalic acid solution is measured into the mixture, and the excess of oxalic acid determined by titration with the standard permanganate solution. Van Sandt (8) has recently developed a polarographic method for determining atmospheric acrolein adsorbed on silica gel. The method is specific for acrolein and the common aldehydes do not interfere.

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## ACRYLONITRILE

### Characteristics

Acrylonitrile, vinyl cyanide, propene nitrile,  $\text{CH}_2=\text{CHCN}$ , is a stable, colorless, mobile liquid having an ethereal, not unpleasant, odor when pure. The commercial product has a smell somewhat resembling phosphorus. Its more important physical properties (1) are as follows: boiling point,  $77.3^\circ \text{C}$ .; freezing point,  $-83^\circ \text{C}$ .; density at  $25^\circ \text{C}$ ., 0.8004; index of refraction,  $n_{25/D}$  1.3884; solubility in water at  $25^\circ \text{C}$ ., 7.4 per cent by weight; flash point,  $0^\circ \pm 2.5^\circ \text{C}$ .; inflammable limits in air, lower limit, 3.05 per cent and upper limit, 17 per cent by volume. Acrylonitrile is soluble in all proportions in acetone, benzene, carbon tetrachloride, ethylalcohol, and a number of other organic solvents. While it is obvious that chemically acrylonitrile is simply ethylene,  $\text{CH}_2=\text{CH}_2$ , with one of the hydrogen atoms replaced by the cyanide radical, the commercial manufacture is somewhat more involved. Commercially ethylene oxide is converted to ethylene cyanohydrin ( $\text{CH}_2\text{OH}-\text{CH}_2\text{CN}$ ) which in turn is dehydrated to acrylonitrile.

### Industrial Uses

The unsaturated character of the acrylonitrile molecule makes it well suited for polymerization reactions, and it is because of this property that it is used in the synthesis of rubber-like materials and thermoplastic resins. The synthesis of Buna N type artificial rubber involves the use of this substance. While this type of synthetic rubber is more expensive to produce than other types, such as Buna S, its properties are such that it has become a synthetic rubber of considerable importance. This is chiefly due to its oil-resistant properties. During the war, it was particularly useful for self-sealing gasoline tanks on aircraft. Acrylonitrile is an important intermediate for chemical syntheses in which its chemical reactivity is utilized. It undergoes a condensation action with reactive ketones to provide a wide variety of ketonic poly-nitriles and polycarboxylic acids. Acrylonitrile is of some importance in the aging of

viscose. It has a solubilizing action and causes an immediate rise in "salt index" (2). The production of acrylonitrile in the United States amounted to 63,107,000 pounds in 1954.

### Toxicity

Dudley (3, 4, 5) has made a careful investigation of the toxicology of acrylonitrile using guinea pigs, rabbits, cats, dogs, and monkeys as experimental animals. These studies clearly indicate that acrylonitrile is a toxic compound comparable in its toxicity to a molecular equivalent of hydrocyanic acid. The animals were exposed to known concentrations of acrylonitrile and it was shown that the minimal fatal concentration over a 4-hour period for rats was 635 parts per million, while for dogs the minimal lethal concentration was 110 parts per million (3). Dudley's experiments show that repeated exposures to 153 parts per million of acrylonitrile in air are definitely toxic to guinea pigs, rats, and rabbits, while this concentration is much more toxic to monkeys and cats. Dogs represented the most susceptible species of animals studied. These exposures produced irritation of the eyes and nose, loss of appetite, and an incapacitating weakness of the hind legs from which the animals recovered relatively rapidly. Even with exposure to such high concentrations, no definite evidence of accumulative action was observed (4). A significant increase in serum thiocyanate was found immediately following the exposure period and an increase in urine thiocyanate content 24 to 48 hours following the exposure period. In the manufacture of synthetic rubber, acrylonitrile presents definite hazards of vapor toxicity and of toxic absorption. Wilson (6) found that in spite of all precautions to prevent human exposure in a factory some workmen were exposed to mild concentrations. These workmen presented symptoms of nausea, vomiting, and weakness, while headache, fatigue, and diarrhea also occurred in some workers. In several cases, a mild jaundice appeared which lasted for several days and in one case there was severe jaundice. Although no fatal cases occurred in industry, it is felt that sufficient exposure



either to the vapor or through skin absorption would cause death. Schwartz (7) states that dermatitis may occur from acrylonitrile. Mallette (8) enumerates a number of potential exposures to acrylonitrile in the present day Buna N manufacturing process of which the greatest is exposure to fumes vaporized by the heat of driers. Although Ghiringhelli (9) concluded that the mechanism of poisoning by acrylonitrile does not involve the liberation of hydrocyanic acid within the body, Brieger and his associates (10) were able to demonstrate cyanide and cyanmethemoglobin in the blood, proving that the toxic action of acrylonitrile is based on the formation of cyanide in the body. On the basis of his investigation, Dudley recommended a maximal allowable concentration of 20 parts per million in air.

### Analysis

Lawton *et al.* (5) found that none of the present chemical and physical methods for determining acrylonitrile in air was accurate for low vapor concentrations. However, the Rayleigh-Jeans interference refractometer was found satisfactory for concentrations above 90 parts per million. The characteristic odor of acrylonitrile is a useful warning property but owing to olfactory sense fatigue it is only useful for first impressions. Analysis of urine specimens for thiocyanate content of workers exposed to this vapor may be useful in determining exposure. However, care must be used in appraising such data since smoking raises the thiocyanate content of urine just as acrylonitrile does. Petersen and Radke (11) have recently developed a method for the determination of acrylonitrile in air which depends upon quantitative conversion of the nitrogen to ammonia, distillation, and subsequent titration. This method was found to be accurate to concentrations as low as 25 parts per million.

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## THE ALKYL BENZENES

### Characteristics

The lower homologues of benzene are insoluble in water but miscible with absolute alcohol and ether. As the molecular weight increases they become less soluble in alcohol but continue to be somewhat soluble in ether. They are mutually soluble. With increasing molecular weight there is in general a rise in boiling point.

### Uses

The alkylbenzenes are used extensively as solvents for grease, rubber, and resins and for a host of other applications in industry. Their derivatives are used in the manufacture of synthetic dyes, drugs, explosives, and plastics. The production of alkyl aromatics, distillates, and solvents from petroleum in the United States in 1954 amounted to 520,286,000 pounds.

### Toxicity

Toxicological studies of toluene, xylene, ethylbenzene, styrene, diethylbenzene,  $\alpha$ -methylstyrene and vinyltoluene in com-

parison with benzene were recently made by Wolf and his associates (1). The oral LD<sub>50</sub> values for rats were all above 1 gram per kilogram of body weight. These substances were found to be slightly to moderately irritating to the skin of rabbits, but were not absorbed in acutely toxic amounts. Repeated oral doses to rats by intubation 5 days weekly for a period of 6 months demonstrated benzene to be markedly more toxic than toluene, ethylbenzene, isopropylbenzene, and styrene. Exposure to the vapors of benzene, ethylbenzene, styrene,  $\alpha$ -methylstyrene and vinyltoluene using rats, guinea pigs, rabbits and monkeys for a period of 6 months showed benzene to be more toxic than the other substances. Benzene was the only one of these compounds that had an effect on the hematopoietic system.

Both the above animal studies and the results of human exposure indicate the probability that vapor concentrations of styrene,  $\alpha$ -methylstyrene and vinyltoluene which can be voluntarily tolerated by most persons will not cause adverse systemic effects. However in order to avoid complaints of disagreeable odor intensity and eye and nose irritation, a recommended maximum allowable concentration value in workrooms for styrene,  $\alpha$ -methylstyrene and vinyltoluene is 100 parts per million.

Smith and his associates (2) found that when toluene was administered orally to rabbits (350 milligrams per kilogram) 18 per cent of the dose was eliminated unchanged in the expired air. No extra glucuronic acid was excreted, while other monosubstituted benzenes caused an increased glucuronic acid excretion. With ethylbenzene biological hydroxylation occurs and it is excreted as methylphenylcarbinol. Parke and Williams (3) have shown that rats fed labeled benzene (0.15 to 0.5 grams per kilogram) excrete 6 to 8 per cent as phenylglucuronide and 11 to 14 per cent as phenylsulfuric acid.

Gerarde (4) has investigated the toxicity of a number of pure alkylbenzenes and several commercial alkylbenzene solvent mixtures. The pure compounds were normal and branched chain C<sub>1</sub> to C<sub>4</sub> mono-, di-, tri-, and tetra-alkylbenzenes. The hydrocarbons mixed with an equal volume of olive

oil were administered subcutaneously to rats at a dosage of 1 milliliter of hydrocarbon to 1 kilogram of body weight. Benzene was the only substance which caused loss of body weight, leucopenia, and a decrease in the total femoral marrow cell population. In the alkylbenzene-treated groups, the leucocyte count, thymus and spleen weights, and total femoral marrow cell population and nucleic acid were normal or increased. The difference in response to benzene and the alkylbenzenes is attributed to the chemical differences of the metabolites formed. Whereas phenolic compounds are the principal metabolites of benzene, the alkylbenzenes are converted into alcohols or carboxylic acids by side chain oxidation. The latter have a low order of toxicity and do not affect cell production. It is suggested that the introduction of one or more alkyl groups on the benzene nucleus so changes the unique myelotoxic effect of benzene that the substituted compound is no longer myelotoxically active.

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### •ALLYL ALCOHOL

#### Characteristics

Allyl alcohol, vinyl carbinol, 2-propen-1-ol, 1-propenol-3,  $\text{CH}_2=\text{CHCH}_2\text{OH}$ , is named from the Latin *allium* (garlic) because the allyl radical,  $\text{CH}_2=\text{CHCH}_2-$ , is found in garlic as a sulfur compound. It is a colorless neutral liquid with an irritating odor. It boils at 96 to 97° C., melts at -129° C., has a density of  $d_{20/4}$  0.8540 and an index of refraction of  $n_{20/D}$  1.41345. Allyl



alcohol is prepared by distilling glycerol with oxalic acid at a temperature of about 260° C. Acid oxalic ester of glycerol is first formed and decomposes at a higher temperature to yield allyl alcohol, carbon dioxide and water. A small amount of allyl alcohol is obtained in the distillation of hardwood for charcoal—about 180 milliliters per ton of dry wood. Allyl alcohol is miscible with water, alcohol and ether in all proportions. It has the properties of a primary alcohol and of an unsaturated compound, i.e., it forms esters, yields acrylic acid on mild oxidation, and is oxidized by cold permanganate to glycerol.

### Uses

Allyl alcohol is a commercially important substance used in a number of synthetic reactions. In addition to the preparation of various allyl compounds, it is used in the manufacture of resins and plasticizers.

### Toxicity

Allyl alcohol is very irritating to the skin of mice according to Sander (1) and is considered to be far more toxic than methanol according to Atkinson (2). The latter found that when allyl alcohol was administered to dogs by mouth death occurred within 7 hours following vomiting, convulsive movements, and coma. There was marked irritation of the gastric mucosa. McCord (3) found an exposure of 1,000 parts per million of air was fatal to various laboratory animals, while 200 parts per million after 1 hour caused nasal irritation and obvious discomfort. Rats exposed to allyl alcohol vapor in a concentration of 50 parts per million for 7 hours daily died after an average of 30 such exposures. According to McCord 50 parts per million will cause severe conjunctivitis and lachrymation in man and even 5 parts per million will cause some irritation. The principal toxic effects of allyl alcohol are pulmonary edema, hemorrhages, severe inflammation of the gastrointestinal tract, diarrhea and nephritis with hematuria. Carpenter *et al.* (4) found the LC<sub>50</sub> value for rats exposed to the vapor of allyl alcohol to be 0.6 milligrams per liter of air.

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## ALLYL CHLORIDE AND ALLYL BROMIDE

### Characteristics

Allyl chloride, chlorallylene, 3-chloropropene,  $\alpha$ -monochlorpropylene,  $\text{CH}_2=\text{CH}-\text{CH}_2\text{Cl}$ , is a colorless liquid having a boiling point of 44.6° C., melting point 136.4° C., density  $d_{20/4}$  of 0.938, and index of refractions of 1.41538. Allyl chloride possess an unpleasant pungent odor, is nearly insoluble in water, but is completely miscible with alcohol, ether, chloroform, and petroleum ether. The unsaturated nature of this substance and the mobility of the chlorine group, which may be replaced by other groups, such as OH,  $\text{NH}_2$ , CH, etc., makes it particularly suitable as a starting point for the synthesis of compounds of the general type  $\text{CH}_2=\text{CHCH}_2\text{X}$ . Allyl chloride is made from the unsaturated allyl alcohol either by the action of phosphorus trichloride or simply by esterification with hydrogen chloride. Further chlorination yields glycerol trichlorohydrin having a boiling point of 155° C. The dibromide boils at 195° C.

Allyl bromide, bromallylene,  $\alpha$ -monobromopropylene, 3-bromo-1-propene, 3-bromopropene,  $\text{CH}_2=\text{CHCH}_2\text{Br}$ , is a colorless liquid having an unpleasant odor, a boiling point of 70 to 71° C., density  $d_{20/4}$  of 1.398, and index of refraction of  $n_{20/D}$  of 1.4655. It is only slightly soluble in water but dissolves in alcohol, ether, carbon disulfide, and carbon tetrachloride.

### Industrial Uses

While production figures in the United States for allyl chloride are not at present available, the analogous allyl bromide was represented in 1941 by a sales quantity of

52,737,000 pounds. While the principal use of both the chloride and bromide has been the manufacture of synthetic perfumes and for other organic syntheses, more recently allyl chloride has been used in copolymerization reactions with styrene in the production of synthetic resins and plastics.

### Toxicity

Adams, Spencer, and Irish (1) found allyl chloride to be among the most toxic of the halogenated aliphatic hydrocarbons. It possesses a very strong irritant action and rats and guinea pigs exposed to concentrations in air varying from 10 to 100 milligrams per liter showed irritation of the mucous membranes within a few minutes. The narcotic action on the other hand appears to be very weak. While pathological examination showed the presence of significant lesions in the lung and kidneys, only slight changes in the liver had occurred. Death was ascribed to lung injury, although renal damage may also have occurred from prolonged exposures at low concentrations. Surviving animals recovered completely. Death of experimental animals has been caused by concentrations of allyl chloride as low as 1 milligram per liter for an exposure of 4 hours, according to Henderson and Haggard (2).

Allyl bromide, according to Flury and Zernik (3), is an active irritant to the mucous membrane of the eyes and respiratory passages and causes dizziness, headache, and lung irritation. No industrial poisoning has been recorded with reference to either allyl chloride or allyl bromide. No maximum allowable concentration value has been established for either of these compounds.

### Analysis

No specific method has been developed for the determination of the vapor of allyl chloride or allyl bromide in air as contaminants. In view, however, of the reactivity of the compounds and ease of replacement of the halogen group, no particular difficulty should be encountered with reference to their detection and estimation. The general methods applicable to determinations of the halogenated hydrocarbons may be used or the recently developed procedure of Setter-

lind (4) for the determination of chlorinated hydrocarbons in industrial atmospheres may be applied.

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## THE AMINOPHENOLS

### Characteristics

The aminophenols are of considerable physiological interest as well as of industrial importance. *o*-Aminophenol (*o*-hydroxyaniline, or 1-hydroxy-2-aminobenzene) melts at 173° C., is moderately soluble in water (2 grams per 100 milliliters) and alcohol (4.35 grams per 100 milliliters), soluble in ether, yields a red color with ferric chloride and sublimes somewhat readily. *m*-Aminophenol (1-hydroxy-3-aminobenzene), the least important of the aminophenols, melts at 122 to 123° C., is moderately soluble in hot water, soluble in alcohol and in ether and is sparingly soluble in benzene and ligroin. It is relatively more stable in air than its isomers. The production of the *m* derivative in the United States in 1951 amounted to 619,000 pounds. *p*-Aminophenol (1-hydroxy-4-aminobenzene, rodinal, or ursol P) is by far the most important of the amino-hydroxybenzenes so far as industrial use is concerned. Production of this substance and its salts in this country in 1951 was 859,000 pounds. The white leaflet crystals of *p*-aminophenol have a melting point of 184° C. (with partial decomposition), are sparingly soluble in cold water (1.1 grams per 100 milliliters); (4.5 grams per 100 milliliters cold alcohol); and sublime with partial decomposition. *p*-Aminophenol is soluble in alkalis, the solution rapidly turning violet in color. The aminophenols are prepared by the reduction of nitrophenols and



nitrosophenols. Tin and hydrochloric acid effect a complete reduction of the nitro group. *p*-Aminophenol is prepared by the reduction of either *p*-nitrophenol,  $\beta$ -phenylhydroxylamine, or by heating *p*-chlorophenol with ammonia in the presence of copper. The aminophenols (*o*, *m*, and *p*) crystallize as white or colorless crystals when pure, but the commercial product is either gray or brownish in color, owing to slight surface oxidation.

### Uses

The aminophenols are used in the manufacture of azo and sulfur dyes, and are applied in the arts to the dyeing of furs, hair and leather. *p*-Aminophenol is used as a photographic developer, owing to its stability in solution, and is marketed under various names, such as Rodinal, Azol, and Certinal.

### Toxicity

The toxicity of the aminophenols is not marked. Compared with certain other aromatic amines, *p*-aminophenol in particular is relatively less toxic. For instance, the administration of doses of 3.5 grams per kilogram of body weight of *p*-aminophenol to rabbits produced no pronounced appearance of poisoning, while 1.0 to 1.5 gram per kilogram of body weight of aniline similarly administered caused death (Rohde, 1). Following the intravenous injection of *p*-aminophenol, methemoglobinemia is somewhat slowly produced in various species of animals. Heubner (2) investigated the three aminophenols with reference to the speed of methemoglobin formation *in vitro* and found that the quickest response was made with *o*-aminophenol. *p*-Aminophenol formed methemoglobin more slowly in comparison, and the *m*-compound was found to be the least effective. It was also shown by *in vivo* experiments that *m*-aminophenol is less toxic than the *o*- or *p*-forms. A suggested explanation of the relative nontoxicity to the whole animal of *p*-aminophenol is that only the oxidized form is active. When injected, or produced in the animal (as a means of detoxication), it must remain in the reduced form, although the formation of methemo-

globin shows that some is present in the quinoneimine form (3). There is some evidence, as shown by Michel *et al.* (4), to indicate that aniline arising from acetanilide in the body can be oxidized to *p*-aminophenol. However, Brodie and Axelrod (5) found that free *p*-aminophenol is not found in the urine following the administration of acetanilide. Instead, the *p*-aminophenol is conjugated and excreted as *N*-acetyl-*p*-aminophenol and the analgesic effect of acetanilide is indeed due to this derived product (6).

Williams (7) found that aminophenylglucuronides are produced in the animal body in response to the administration of the aminophenols. In the case of *p*-aminophenol, hydrated *p*-aminophenyl- $\beta$ -glucuronide ( $C_{12}H_{15}NO_7 \cdot H_2O$ ) is formed and, unlike its analogous isomers, it has a definite melting point (213° C., with decomp.). The neutralized *o*- and *p*-aminophenylglucuronides form methemoglobin *in vitro* and the *o* compound appears to be several times as effective as the *p*. A slight formation of methemoglobin occurs with the *m* derivative, although *m*-aminophenol itself appears to be ineffective. In the case of *p*-aminophenol about 8 per cent of the amount of aminophenol fed is excreted as glucuronide in the urine and, unlike the case with the *o* and *m* derivatives, free *p*-aminophenol is present in the urine. Hildebrand and Marquardt (8) have recently investigated the toxicity of *m*-aminophenol, which is one of the metabolites of *p*-aminosalicylic acid used in the treatment of tuberculosis. The  $LD_{50}$  for white mice (intraperitoneally) after 24 hours was found to be 102 milligrams per kilogram of body weight for *m*-aminophenol.

### Analysis

The method of determination of *p*-aminophenol originally used by Hinsberg and Treupel (9) is based on the indophenol reaction in which a color is formed when the *p*-aminophenol solution is treated with chromic acid and phenol. The addition of a few drops of ammonia changes the red color to blue. The depth of color and hence the *p*-aminophenol content was judged by com-

parison with known concentrations of the pure compound. Greenberg and Lester (10) determined small amounts of *p*-aminophenol in urine by coupling it with  $\alpha$ -naphthol in alkaline solution. A bright blue pigment is formed which has a strong light absorption at 620 millimicrons and its density is directly proportional to the amount of *p*-aminophenol present. Brodie and Axelrod (5) separated free *p*-aminophenol from biological material by extraction with ether. It was then coupled with phenol in acid solution and an indophenol dye formed with sodium hypobromite. The *p*-aminophenol content was then evaluated spectrophotometrically. More recently various methods for the determination of *p*-aminophenol were reviewed by Ballard (11) and an especially sensitive and precise method developed which depends upon its reaction with *p*-dimethylaminobenzaldehyde.

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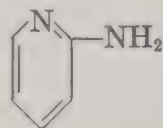
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of *p*-aminophenol in *p*-methyl-aminophenol sulfate. Analyst 75: 430 (1950).

## 2-AMINOPYRIDINE

### Characteristics

2-Aminopyridine,  $\alpha$ -aminopyridine,  $\alpha$ -pyridylamine,  $C_5H_6N_2$ ,



is a crystalline substance having a melting point of 56° C. Its boiling point is 204° C. By careful heating it can be sublimed. It is readily soluble in most organic solvents, particularly ligroin, from which it may be crystallized. 2-Aminopyridine is prepared from 2-chloropyridine by heating with zinc chloride and ammonia to 220° C. It may also be prepared by heating pyridine with sodamide. The pure substance has a somewhat bitter taste and an anesthetic action. With picric acid it forms a picrate, appearing as yellow needles melting at 216 to 217° C. and very difficultly soluble. The dibenzoyl derivative, prepared by melting together 2-aminopyridine with benzoic acid anhydride, crystallizes from alcohol in the form of needles melting at 165° C., insoluble in water, difficultly soluble in cold alcohol and easily soluble in ether and in benzene. It dissolves in strong acids with decomposition.

### Uses

2-Aminopyridine is used principally in the manufacture of pharmaceutical preparations, especially antihistamine drugs.

### Toxicity

2-Aminopyridine in vapor form strongly inhibits the growth of *aspergillus* (1) and shows pronounced growth inhibitory effects on plants in general (2). It has been used as a fungicide for preventing the decay of citrus fruit (3). When injected subcutaneously in frogs, and either subcutaneously or intravenously in cats, 2-aminopyridine is toxic in doses of 2 milligrams. In cats it causes strychnine-like convulsions, and it also has



an anesthetic action on both cats and rabbits, according to Efimov and Bednyagina (4). Similar results had previously been reported by Dingemanse (5) who also found that 2-aminopyridine produces an anesthetic action on the frog's skin. It does not have any action on the rabbit's cornea and in general it produces similar effects to those of  $\beta$ -nicotine. In the pigeon, Mouriquand *et al.* (6) found the border line of intoxication by ingestion to be 12.5 milligrams. Convulsions and death resulted from doses of 15 milligrams. Watrous and Schulz (7) report a case of industrial exposure in which a worker was exposed for 5 hours to an atmosphere containing approximately 5.2 parts per million of 2-aminopyridine. This exposure produced headache, nausea, cutaneous flushing, and transient hypertension. Spolyar (8) was the first to report a fatal case of poisoning in industry from this substance in this country. In this case an 18-year-old employee in charge of a fractionating column spilled a bucket of liquid 2-aminopyridine over his arms and lower extremities. He continued to work for 1½ hours and then developed dizziness, headache, and difficulty in breathing. He finally became unconscious and died. In this case it was thought that the respiratory hazard should be considered in addition to skin absorption.

### Analysis

A direct titrimetric method and a modified Kjeldahl method can be used for the estimation of 2-aminopyridine in citrus fruit (9). A later method (7), based on the color formed when 2-aminopyridine is heated in the presence of quinone and acetic acid, is especially applicable to the analysis of air samples containing the dust or vapor of this substance. A currant-red to violet-red color is produced and is stable for several hours. Time and temperature are important in the development of this color and careful comparison should be made with known amounts of 2-aminopyridine within the range of determination.

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## AMYL ACETATE

### Characteristics

The amyl acetate of commerce which is mostly derived from the amyl alcohols of fused oil or is prepared synthetically from *n*-pentane and isopentane consists largely of a mixture of isoamyl and normal amyl acetates, the former predominating. A certain amount of secondary amyl acetate is found in commerce. *n*-Amyl acetate,  $\text{CH}_3\text{CO}_2\text{C}_5\text{H}_{11(n)}$ , boils at 149.25° C., melts at -70.8° C., has a density of  $d_{20/4}$  0.8756, and index of refraction  $n_{20/D}$  1.4031. The saponification equivalent is 130, and on hydrolysis it yields normal amyl alcohol and acetic acid. isoAmyl acetate,  $\text{CH}_3\text{CO}_2\text{C}_5\text{H}_{11(i)}$ , boils at 142° C., has a density of  $d_{20/4}$  0.8674, and an index of refraction  $n_{20/D}$  of 1.40034. The saponification equivalent of this ester is 130. Secondary amyl acetate,  $\text{CH}_3\text{CO}_2\text{C}_5\text{H}_{11(\text{sec})}$ , boils at 133.5° C., has a density of  $d_{18/4}$  0.8692, and an index of refraction  $n_{20/D}$  of 1.3960. The saponification equivalent of this ester is 130. On saponification, it yields pentanol-2 and acetic acid. All the above esters may for convenience be grouped under the heading of

"amyl acetate" and in the purified state are clear, colorless liquids with a pleasant ethereal odor in low concentrations. The concentrated vapor, however, is pungent and disagreeable. The commercial amyl acetate is a yellow liquid with similar but more pronounced odor because of various impurities.

### Industrial Uses

Amyl acetate is an important industrial solvent and the total production of the United States during 1953 amounted to 8,302,000 pounds (1). During that year, 50 per cent of the total amyl alcohol produced was allocated to the manufacture of amyl acetate. The principal outlet for amyl acetate is that of solvent for nitrocellulose and in the preparation of varnishes and lacquers. A certain amount is used in flavoring because of its banana-like or pear-like flavor and odor. It enters into a variety of industrial processes, such as the manufacture of artificial leather, silk, or pearls, photographic film, celluloid cements, waterproof varnishes, and bronzing liquids. A special grade of amyl acetate is used for fuel in the Hefner lamp which is employed as a photometric standard.

### Toxicity

There is no information available to indicate that the various amyl acetates differ particularly with reference to physiological response. Patty, Yant, and Schrenk (2), in a study of secondary amyl acetate, found that the principal symptoms following exposure were those of eye and nasal irritation and narcosis. At room temperature, no concentration was attained which was dangerous to life in 30 to 60 minutes. Exposure to 0.5 to 1.0 per cent of the vapor for several hours, however, is considered dangerous. The maximum concentration in which exposure may occur for several hours in the case of guinea pigs was 0.2 per cent. Flury (3) states that a concentration of 5 milligrams per liter or about 900 parts per million could be endured by man for  $\frac{1}{2}$  hour. In a few cases, symptoms of gastrointestinal disturbance have been reported (4, 5) and some indication has been noted of irritation of the liver following exposure (6). The latter investigators observed urobilinuria following exposure to

amyl acetate. Smyth and Smyth (7), however, as the result of study of various lacquer solvents, found that amyl acetate was not damaging in comparison with other lacquer solvents and concluded that amyl acetate was among the safest of the solvents studied.

Any anesthetic effect following inhalation of amyl acetate vapor is undoubtedly due to the alcohol produced by hydrolysis in the body. Baldi (8) found that amyl acetate caused conjunctival irritation, sensitivity to the odor, a feeling of oppression in the chest and cough in men exposed to air containing 20 to 60 milligrams per liter.

### Analysis

Methods applicable to the analysis of amyl alcohol may be similarly employed for the determination of amyl acetate as a contaminant of air. Korenman's method has been particularly recommended for this purpose and is based on the production of a pink to violet-red coloration on the addition of furfural and concentrated sulfuric acid to the suspected sample (9). Custance and Higgins (10) have reported a colorimetric procedure for amyl acetate, based on its reaction with *p*-dimethylaminobenzaldehyde, which is accurate for air samples containing as little as 10 parts per million.

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## AMYL ALCOHOL

## Characteristics

Amyl alcohol,  $C_5H_{11}OH$ , molecular weight 88.11, also known as fusel oil, grain oil, potato spirit, or amyl hydroxide, is a colorless

TABLE 1

Substance	Formula	Melting Point °C.	Boiling Point °C.	Density $D_{20/4}$	Index of Refraction $n_{20/D}$
<b>Primary</b>					
1-pentanol (normal amyl alcohol, butylcarbinol)	$CH_3-CH_2-CH_2-CH_2-CH_2OH$	-78.5	138.0	0.81479	1.4077 $n_{25/D}$
2-methyl-1-butanol (d-amyl alcohol, sec. butylcarbinol, 2-methyl-butan-1-ol)	$CH_3-CH_2-\underset{\substack{  \\ CH_3}}{CH}-CH_2OH$		128.9	0.8193	1.4107
3-methyl-1-butanol (iso-amyl alcohol, primary isobutylcarbinol, 2-methyl-butan-4-ol, 3-methyl-butan-1-ol)	$CH_3-\underset{\substack{  \\ CH_3}}{CH}-CH_2-CH_2OH$	-117.5	132.0	0.80918	1.40851 $n_{15/D}$
2,2-dimethylpropanol (isobutylcarbinol, tert. butylcarbinol)	$\begin{array}{c} CH_3 \\   \\ CH_3-C-CH_2OH \\   \\ CH_3 \end{array}$	-52.0	113.0		
<b>Secondary</b>					
2-pentanol (sec. amyl alcohol, methylpropylcarbinol, 1-methyl-1-butanol, pentan-2-ol)	$CH_3-CH(\underset{\substack{  \\ OH}}{OH})-CH_2-CH_2-CH_3$		119.85	0.80919	1.4060
3-pentanol (diethylcarbinol, 1-ethyl-1-propanol, pentan-3-ol)	$CH_3-CH_2-\underset{\substack{  \\ OH}}{CH}-CH_2-CH_3$		116.1	0.82037	1.4103
2-methylbutanol-3 (methylisopropylcarbinol, 1,2-dimethyl-1-propanol, 3-methylbutan-2-ol)	$CH_3-\underset{\substack{  \\ CH_3}}{CH}-\underset{\substack{  \\ OH}}{CH}-CH_3$		112.0	0.818	1.3973
<b>Tertiary</b>					
2-methyl-2-butanol (tertiary amyl alcohol, dimethylethylcarbinol, amylene hydrate, 1,1-dimethyl-1-propanol, 2-methyl-butan-2-ol)	$\begin{array}{c} CH_3 \\   \\ CH_3-C-CH_2-CH_3 \\   \\ OH \end{array}$	-8.55	102.35	0.80889	1.4052

liquid of density 0.870, melting point  $-134^{\circ}\text{C}$ ., and boiling point  $137.5^{\circ}\text{C}$ . There are eight isomeric amyl alcohols, three existing each in two modifications. Commercial amyl alcohol is a mixture of several isomeric alcohols and has a pungent and penetrating odor.

The eight primary, secondary, and tertiary alcohols have, in brief, the characteristics shown in Table 1.

In the fermentation of cereals, potatoes, and other materials, one of the by-products is fusel oil. This is separated by fractional distillation. Amyl alcohol occurs in the fusel oil fraction. Synthetic amyl alcohol is obtained by chlorinating pentane, which is a low boiling fraction of casing-head gasoline. The chloropentane thus obtained is then hydrolyzed and yields normal amyl alcohol. Amyl alcohol derived from fusel oil is a mixture of *iso*amyl alcohol and optically active (*dextro*) amyl alcohol.

### Industrial Uses

During 1945, 13,773,000 pounds of the amyl alcohols were produced in the United States. In allocations in the war program, approximately 50 per cent was used in the manufacture of amyl acetate, 28 per cent in lacquers and solvents, 9 per cent for ore flotation reagents, 5 per cent for drugs and pharmaceuticals, and the remainder for adhesives, petroleum refining, and other miscellaneous uses (1). The total production of crude and refined amyl alcohols in 1953 was 20,770,000 pounds.

### Toxicity

The local irritating action of the amyl alcohols on mucous membranes causes nausea, vomiting, irritation of the throat, lacrimation, and conjunctivitis. There is headache and vertigo which progresses to stupor and collapse if the dosage is large. Zangger (2) has noted two fatal cases in men who were engaged in painting the inside of a container with Zapon lacquer which contained amyl alcohol. Two other men engaged in rescuing them were rendered unconscious. Flury and Zernik (3) describe the following symptoms in man resulting from inhalation of air contaminated with amyl alcohol vapor: ir-

ritation of mucous membrane of eyes and nasal and respiratory passages, rushing of the blood to the head, headache, giddiness, nausea, diarrhea. The excretions, as well as the perspiration, smell of amyl alcohol. Haggard and his associates (4) determined the comparative toxicities of the primary, secondary, and tertiary amyl alcohols on the basis of basic lethal amounts, *i.e.*, the amount as grams per kilogram when present in the body which yields that concentration in the blood which causes respiratory failure. It consisted of the repeated intraperitoneal administration of decreasing amounts of the substance under test until death resulted after which the concentration of the substance in the venous blood was determined. The basic lethal amount present in the blood was found to be 0.61 gram per kilogram for 1-pentanol, 2-methyl-1-butanol (*laevo*), and 3-methyl-1-butanol. These alcohols have a basic toxicity 12 times as great as that for ethyl alcohol. The corresponding values for 2-methyl-1-butanol (*racemic*) are 0.88 gram per kilogram, and for 2-methyl-2-butanol 1.53 gram per kilogram. A modification of this procedure indicates that the secondary alcohols have a basic toxicity lower than the primary alcohol but higher than the tertiary.

### Analysis

Korenman (5) has developed a method for determining the amount of amyl alcohol vapor in the air of factories. The method, in brief, consists in adding 20 milliliters of ethyl alcohol diluted with an equal volume of water to a sample of air collected in a dry flask of known capacity. To 1 milliliter of this solution and 0.1 ml. of a 1 per cent furfural solution, 1.5 milliliter of concentrated sulfuric acid is added and layered beneath the chilled solution. A pink to violet-red color is produced depending upon the amyl alcohol concentration. Color standards of known concentrations of amyl alcohol are similarly prepared for comparison. Salicylic aldehyde with amyl alcohol and sulfuric acid likewise forms a color suitable for colorimetric determination. *iso*Amyl alcohol with a similar procedure yields a raspberry color with *p*-hydroxybenzaldehyde. *p*-Diaminobenzal-



dehyde is said to give somewhat more exact results than salicylic aldehyde. The application of this reaction is discussed in detail by Penniman, Smith, and Lawshe (6).

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### ANILINE

#### Characteristics

Aniline, aminobenzene or phenylamine, an arylamine, has the composition  $C_6H_5NH_2$  and a molecular weight of 93.12. It is a colorless or slightly brownish liquid darkening with age and having a boiling point of  $184.32^\circ C.$ , density 20/4 1.0219, freezing point  $-6.24^\circ C.$ , and index of refraction  $n_{20/D}$  1.58629. Aniline has a characteristic odor and burning taste, is inflammable, and is volatile with steam. One gram dissolves in 28.6 milliliters of water at room temperature and in 15.7 milliliters of boiling water. It is miscible with benzene, alcohol, chloroform, and most other organic solvents and combines with acids to form salts. It dissolves the alkali metals evolving hydrogen and forming anilides, such as  $C_6H_5NHNa$ . While aniline was originally prepared by distillation of indigo with an alkali, it is manufactured on the large scale from benzene by nitration of the latter, followed by reduction of the nitrobenzene by iron and hydrochloric acid (1). To some extent, aniline has been produced industrially from nitrobenzene and hydrogen or water gas in the presence of a catalyst. In a more recent

process, aniline is made by treating chlorobenzene with ammonia at high pressures.

#### Industrial Uses

In the United States, 97,349,000 pounds of aniline was produced in 1954. Aniline is used in the organic synthesis of many chemicals, in the manufacture of azo dyestuffs, aniline black and aniline colors in general, as an ingredient in antifouling paints, paint removers, paints and varnishes, as a gelatinizer for nitrocellulose, and as a process material in the manufacture of certain cellulose compounds and plastics. It is a vulcanizing agent and accelerator in the rubber industry. It is a germicide, an ingredient of indelible and other inks, and is a component of many pharmaceutical products. Although used in the past in medicine, it is not recommended at the present time.

#### Toxicity

The poisonous properties of aniline have long been known and a number of fatalities have occurred in the synthetic dye industry where workers have come in contact with this substance. Poisoning in industry is characterized by the formation of methemoglobin, headache, cyanosis, muscular weakness, mental confusion, convulsions and psychic disturbances. Aniline has been shown to produce marked respiratory depression, immediate marked fall in blood pressure, and progressive cardiac arrhythmias, including intraventricular block (2). Clark and his associates (3) have stated that the most important effect of acute aniline intoxication in the dog is the production of methemoglobinemia and indirectly the effects of oxygen deficiency. The application of the recording spectrophotometer to the determination of methemoglobin permits one to follow the effects of aniline absorption (4). According to Lester and his associates (5), methemoglobinemia plays no important part in the acute toxicity of aniline. However, in poisoning with similar compounds, such as 2-anilinoethanol, methemoglobinemia is directly related to the cause of cyanosis (6). In most cases, aniline poisoning in industry occurs from inhalation of the vapor or from skin absorption on direct contact

with the liquid. Rozenberg (7) found blood and urine changes following ingestion to be more pronounced than in occupational poisoning from aniline. In an attempted suicide case in which 100 grams of aniline was taken, a sharp rise in methemoglobin (from 68 to 86 per cent) occurred on the first day; severe instead of very mild hemolysis, as shown by a hemoglobin drop to 30 per cent and an erythrocyte count of 1,400,000; a drop in glutathione; and a higher free phenol content of the urine. Oxyhemoglobin and methemoglobin appeared in the urine on the seventh day. The reported effect of aniline in causing papillomata of the bladder which may become malignant has frequently been noted since the first cases were reported by Rehn (8) in 1895. According to Hunter (9), approximately 550 cases of this type have been recorded in all countries. Goldblatt (10) states that while  $\beta$ -naphthylamine and benzidine are certainly causes of bladder cancer, aniline and  $\alpha$ -naphthylamine are possible causes. He finds, however, that processes for manufacturing aniline are sufficiently controlled at the present time to remove this hazard. Prolonged absorption of small quantities of aniline leads to chronic poisoning which is marked occasionally by vesicular miliaria and other skin eruptions. Certain aniline dyes, though harmless to the skin of most persons, can cause dermatitis with sensitive individuals and dermatitis has been noted from this source from cosmetic preparations (11). Seventeen cases of poisoning were recently reported in babies due to skin absorption of dye from the ink on freshly stamped diapers (1). The detoxication mechanism of aniline poisoning has been studied by Smith and Williams (13) who found that about 8 per cent of the aniline given rabbits by mouth is excreted as ethereal sulfates of *o*- and *p*-aminophenol and 4-aminoresorcinol, while about 70 per cent of the aniline is excreted as glucuronides. Henderson and Haggard (14) state that 7 to 53 parts per million of aniline cause slight symptoms after exposure of several hours. Chronic inhalation tests with experimental animals exposed to aniline vapor by Hackley *et al.* (15) support the present maximum allowable concentration value of 5 parts per million.

## Analysis

Aniline may be identified by the preparation of distinctive substances, such as acetanilide or phenylisocyanide. Acetanilide (melting point 111.7° C.) is formed when aniline is treated with acetic anhydride. On warming with alcoholic potassium hydroxide and chloroform, aniline yields phenyl isocyanide (boiling point 165° C.) which has a characteristic and disgusting odor. With bromine water, aniline yields a precipitate of the tribromo derivative (melting point 118° C.). Quantitatively, aniline may be determined by Elvove's method (16), which is based upon the purplish color developed on the addition of calcium hypochlorite solution. Methyl- or dimethyl-aniline do not give this color when pure. The official method adopted in Great Britain (17) for the determination of aniline vapor in air is similarly based upon the coloration produced with calcium hypochlorite. The test is made more sensitive by the addition of ammonia and phenol. A permanent blue color is produced even by 1 part of aniline in 100,000 parts of air. Riehl and Hager (18) have found that the concentration of aniline vapor in air may be determined within the range of 5 to 150 parts per million by means of paper strips impregnated with a 4 per cent solution of furfural in glacial acetic acid.

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## BENZENE

### Characteristics

Benzene, benzol,  $C_6H_6$ , boiling point  $80.094^\circ C.$ , melting point  $5.51^\circ C.$ , density  $d_{20/4}$  0.87895, and index of refraction  $n_{20/D}$  1.50124, is a colorless liquid with a characteristic odor. It is soluble in water only to the extent of 0.06 part per hundred at  $20^\circ C.$ , but is miscible with organic solvents. Its flash point is from  $-12^\circ C.$  to  $-10^\circ C.$  and ignition may be caused by open flames or sparks from electrical appliances. The "light oil" from the fractional distillation of coal tar consists principally of the hydrocarbons—benzene, toluene, xylene, and "solvent naphtha". On nitration, benzene yields both nitrobenzene with a boiling point of  $209^\circ C.$  and *m*-dinitrobenzene with a melting point of  $90^\circ C.$  On bromination, benzene yields bromobenzene, boiling point  $157^\circ C.$  and *p*-dibromobenzene, melting point  $89^\circ C.$  When heated with bromine plus iron catalyst, it yields mainly *p*-dibromobenzene. It forms a picrate of colorless needles, melting point  $83.9^\circ C.$  With  $ClSO_3H$ , it yields benzenesulfonyl chloride, melting point  $14^\circ C.$ ,

boiling point  $251^\circ C.$ , and diphenyl sulfone with a melting point of  $128^\circ C.$  It is slowly sulfonated with boiling concentrated sulfuric acid.

### Industrial Uses

The production of benzene in the United States amounted to 673,715,000 pounds in 1954 (1). During the war, the use of benzene for chemical purposes had increased considerably, while its use for motor fuel dropped correspondingly. Thus in 1945, the total production of benzene for motor fuel amounted to 32,151,532 gallons, while the production of benzene for all other purposes corresponded to 159,013,084 gallons (2). Apart from motor fuels, benzene is mostly used in manufacture of rubber, chemicals, dyestuffs and intermediates, explosives, aniline, phenol, resorcinol, benzidine, picric acid, and miscellaneous organic preparations. It is used as a solvent for oils, fats, waxes, gums, natural and synthetic resins, cellulose esters and ethers, and a large variety of varnishes, airplane dopes, as well as in paint and varnish removers.

### Toxicity

On inhalation in high concentration, benzene is narcotic in action, producing successively euphoria, hypermotility followed by sleepiness, and fatigue. The preliminary excitement is greater than with chloroform and as a general anesthetic, its action is more of a convulsive character. In concentrated form, it is especially toxic and may produce death. In dilute form, the vapors produce headache, vertigo, ataxia, twitchings, convulsions, and coma. Chronic poisoning in industry is characterized by leukopenia and aplastic anemia. Bowers has recently described a chronic case of benzene poisoning with fatal termination characterized by an intractable anemia, leukopenia, and thrombocytopenia following long continued exposure to benzene. In this case, the bone marrow was grossly hyperplastic with extensive areas of extramedullary hemopoiesis (3). It should be emphasized that blood changes alone cannot be accepted as evidence of benzene intoxication in the absence of estimations of benzene as an atmospheric contami-

nant (4). Benzene is absorbed through the skin but clinically detectable benzene poisoning has not been found from this source (5). However, absorption from the skin is of far less importance than absorption from inhalation. A test for detecting active absorption of benzene may be made by determination of the ratio of the total urine sulfates to the inorganic sulfates (6). Since serious trouble may develop following exposure to benzene without any warning symptoms, the significance of neglected disorders is often apparent when too late. Lambin (7) has indicated a procedure for the detection of benzene poisoning applicable to large groups of individuals so exposed.

Teisinger's experiments with men inhaling benzene vapor indicate a lower desaturation rate the longer the inhalation period (8). This is a point of importance in industry, where continuous exposure for long periods may occur. Schildknecht (9) also reports that benzene accumulates in the body, so that recovery is slow after removal from exposure to benzene vapor. Parke and Williams (10) found that rats fed labeled ( $C^{14}$ ) benzene in amounts of 0.15 to 0.50 gram per kilogram of body weight excrete 6 to 8 per cent of the benzene as phenylglucuronide and 11 to 14 per cent as phenylsulfuric acid. Porteous and Williams (11) state that an adequate supply of protein is necessary for workers exposed to benzene vapor, since protein is the main source of sulfur for the mechanism of detoxication.

### Analysis

Methods for the determination of minute amounts of benzene are, at best, methods of approximation only. The chemical methods are colorimetric in character and depend upon nitration and colorimetric evaluation of the reaction products. Various physical methods have been developed for the determination of benzene, such as the gas interferometer method and the combustible gas detector, and are useful when the air contaminant is solely benzene vapor. In contact with a nitrating mixture (equal parts of concentrated sulfuric acid and fuming nitric acid of d. 1.50) in the cold for 30 minutes, benzene is converted into a mixture of the

*o*, *m*, and *p* isomers of dinitrobenzene. The mixture contains about 95 per cent of the *m* isomer. With aldehydes and ketones, the mixed dinitrobenzenes give a violet color in alkaline solution. The *m* isomer in particular gives a color with acetone. In low concentrations of benzene, the color develops within 30 minutes, is stable for 3 hours, and follows Beer's law. Schrenk and his associates (12) have adapted the nitration method to the determination of small amounts of benzene vapor as an air contaminant, using methyl ethyl ketone as reagent. A combined absorption nitration bubbler tube is used in which the benzene is converted to *m*-dinitrobenzene which is then estimated colorimetrically in saline solution with methyl ethyl ketone. Both Baernstein (13) and Dolin (14) have published methods for the determination of benzene in the presence of toluene and xylene, which depend upon oxidation of the nitro derivatives of the two latter substances. The oxidation products of the nitro derivatives of toluene and xylene are colorless under the conditions described and therefore do not interfere with the benzene determination. The Mine Safety Appliance Company aromatic hydrocarbon detector is a useful apparatus for the field determination of benzene vapor.

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## BENZENE HEXACHLORIDE

### (Gamma Hexachlorocyclohexane)

#### Characteristics

Benzene hexachloride, hexachlorocyclohexane,  $C_6H_6Cl_6$ , one of the newer insecticides also known as "BHC", "666", or "lindane" exists in five isomeric forms—the  $\alpha$ ,  $\beta$ ,  $\gamma$ ,  $\delta$ , and  $\epsilon$ . In the pure state, the isomers are well-defined colorless crystals, practically insoluble in water, soluble in organic solvents, and have a bitter taste and practically no odor. The melting points of the isomers are as follows:  $\alpha$ , 157.5 to 158° C.;  $\beta$ , 309° C.;  $\gamma$ , 112.5° C.;  $\delta$ , 138 to 139° C.; and  $\epsilon$  (1), 218.5 to 219.3° C. At 40° C., the vapor pressure of these isomers are  $\alpha$ , 0.06 millimeter of mercury;  $\beta$ , 0.17 millimeters of mercury;  $\gamma$ , 0.15 millimeters of mercury; and  $\delta$ , 0.09 millimeters of mercury. The solubilities of the isomers of benzene hexachloride have been determined in each of 45 organic solvents and the consistently low solubility of the  $\beta$  isomer and also the higher relative solubilities of the  $\gamma$  and  $\delta$  isomers have been noted by Slade (2). Benzene

hexachloride is produced by bubbling chlorine gas through benzene while powerful ultraviolet rays irradiate the mixture. This produces a solution of crude benzene hexachloride containing the various isomers from which the four isomers which are useless as insecticides are eliminated and the  $\gamma$  isomer is concentrated. A process recently reported utilizes dilute caustic during the chlorination reaction and is claimed to increase the yield of the  $\gamma$  isomer to 42 per cent. Crude benzene hexachloride has a strong, musty, persistent odor. The pure  $\gamma$  isomer itself, however, has but very little odor. Benzene hexachloride or 1,2,3,4,5,6-hexachlorocyclohexane,  $C_6H_6Cl_6$ , should not be confused with hexachlorobenzene  $C_6Cl_6$ .

#### Industrial Uses

Benzene hexachloride is a remarkable compound in that it functions as a stomach poison, contact poison, and fumigant and that it is stable in acid and at high temperatures. Since its insecticidal properties are referred to the  $\gamma$  isomer, it is sometimes called gammexane. This isomer has been shown to be highly toxic to a wide range of insects and related pests at low concentrations, while the other isomers are only from one-sixth to one-sixtieth as toxic.

$\gamma$ -Hexachlorocyclohexane is a British war discovery and against certain pests this substance has proved more toxic in laboratory tests than any other insecticide examined (2). Investigation of this insecticide by measuring the amount necessary to kill individual roaches and flies shows that the approximate  $LD_{50}$  for the cockroach is 4.6 milligrams per kilogram and 0.8 milligram per kilogram for the housefly (3).  $\gamma$ -Benzene hexachloride is distinctly more toxic for these insects than DDT. At the 50 per cent mortality level,  $\gamma$ -benzene hexachloride is about nine times as toxic to houseflies as  $p,p'$ -DDT and about 18 times as toxic as the pyrethrins (4). However, it does not possess the long-lasting toxicity of DDT and to overcome this lack of residual strength, it may be combined with DDT for special applications. It is particularly effective against the cotton boll weevil, cotton aphids, and the cotton flea hopper. It is one of the

few compounds that will kill both cattle lice and eggs at the same time. Lice, fleas, flies, mosquitoes, and numerous other insects are readily controlled and current trials indicate that benzene hexachloride has considerable value as a soil insecticide.

### Toxicity

The acute and chronic toxic effects of benzene hexachloride have been investigated by ingestion experiments with rats (2). The amount of the  $\gamma$  isomer by mouth necessary to kill 50 per cent of the animals in 7 days was 190 milligrams per kilogram of body weight. No chronic effects were noted following the administration of benzene hexachloride. The  $\gamma$  isomer was fed to rats in amounts of 10, 20, or 30 milligrams per day for 5 weeks without producing any effect whatsoever. Woodard and Hagan (5), however, reported some liver damage following feeding the  $\gamma$  isomer to dogs for 36 to 49 days, although they fed 100 milligrams of the mixed isomers daily to rats for 2 months without apparent injury. The subcutaneous injection of the  $\gamma$  isomer in amounts of 100 milligrams per kilogram of body weight killed 25 per cent of the animals. Although  $\gamma$ -benzene hexachloride is an effective insecticide and miticide when impregnated into clothing, Horton, Karel, and Chadwick (6) found, in wearing tests on rabbits with cloth impregnated at 2.0 grams per square foot, that typical symptoms of poisoning, including convulsion, occurred. Having ruled out ingestion and inhalation as possible routes of intoxication and having shown that the affected animals absorbed this substance through the skin, they concluded that  $\gamma$ -benzene hexachloride cannot be safely used to impregnate clothing at concentrations that are effective insecticidally. Recent experiments have shown that exposures to sprays of oil-base containing 3 per cent  $\gamma$  isomer killed rats after 11 days of exposure (7). The  $\gamma$  isomer has also been found to be distinctly toxic to fish at concentrations of 1 part per million. So far as toxicity to humans is concerned, it has been stated that the crude isomer is less hazardous from a toxicological standpoint than DDT (7). However, a number of cases of

poisoning have occurred with workers manufacturing or in the application of benzene hexachloride where exposure has been significantly great (8, 9). Though there is obviously a definite need for more work to be done toxicologically, present indications are that it is improbable that such residual quantities of benzene hexachloride as might remain on foodstuffs under conditions of ordinary application will present any hazard.

### Analysis

Daasch (10) has developed an infrared method for the quantitative determination of each of the five isomers in the insecticide. The differences in the spectral absorption of the isomers are sufficiently great to permit the analysis of mixtures and it is estimated that an accuracy of  $\pm 0.5$  per cent can be obtained. Detection of the dust or vapor can be made by means of the flame detector apparatus for halogenated compounds but this method is not specific. The hexachlorocyclohexanes, in general, possess considerable chemical stability. They can be exposed to hot water and light for some time and may be crystallized from hot concentrated nitric acid without decomposition. However, in the presence of alkalies, such as lime water, at 60° C., hydrogen chloride is removed, yielding a mixture of the isomers of trichlorobenzene. It is possible that this type of decomposition could be applied to the determination of benzene hexachloride dust or fume in the absence of other chlorinated compounds. Reith's method (11) for the determination of hexachlorocyclohexane in vegetables consists in reducing the extracted compound with zinc to benzene, and subsequent nitration followed by colorimetric determination of the *m*-dinitrobenzene thus formed. Babina (12) determines the benzene hexachloride content of air by decomposing the air sample followed by nephelometric determination of chloride by silver nitrate.

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## BENZIDINE\*

### Characteristics

Benzidine, 4,4' diaminobiphenyl, *p*-diaminodiphenyl,



is a white crystalline substance which crystallizes from alcohol as silvery flaky crystals having a melting point of 128° C. and a boil-

ing point of 400° C. at 740 millimeters. It is soluble in alcohol and in ether and is soluble in water to the extent of 1 part in 2,447 parts of water at 12° C. While the hydrochloride is also soluble in water, benzidine sulfate is rather insoluble. It dissolves to the extent of only 0.097 gram per liter at 25° C. Benzidine is prepared by the reduction of nitrobenzene, first to azobenzene, and then to hydrazobenzene and followed in turn by intramolecular rearrangement with hydrochloric acid to benzidine. In the technical preparation of benzidine small amounts of diphenylene (*o*-, *p*-diaminobiphenyl) are formed and benzidine is separated by conversion to the insoluble sulfate.

### Uses

Benzidine is used by the dyestuff manufacturers as a raw material for large volume colors for cotton, such as direct black, benzo blue, and Congo red and brown. Certain safety papers for bank checks depend upon benzidine as the agent to reveal alterations. Benzidine is a valuable reagent for analytical purposes. Production in the United States in 1954 amounted to 1,277,000 pounds.

### Toxicity

Benzidine is absorbed through the skin, even as the sulfate, and is toxic. Adler (1) found the toxicity of benzidine for dogs to be 200 milligrams per kilogram of body weight by oral administration. Nausea and vomiting appeared after several hours and, following larger doses, dyspnea, depression, clonic and tonic convulsions, and death occurred. Pathological changes were noted in the spleen and liver; the urine contained glucose and occasionally albumin. Recent investigations by Sciarini, Meigs, and their associates (2, 3, 4) have demonstrated the urinary excretion of benzidine and certain of its metabolites following the exposure of workers engaged in manufacturing benzidine. The principal metabolite found by Sciarini (5) is 3-monohydroxybenzidine. When benzidine was administered intraperitoneally in dogs unmetabolized benzidine was present in the urine and isolated to the extent of 5 to 15 per cent of the dose and

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3-monohydroxybenzidine in amounts ranging from 25 to 50 per cent of the dose.

For a number of years benzidine has been considered as a cause of bladder tumors in workmen (6, 7, 8), but the experimental production of tumors in animals was not successfully demonstrated until 1950 when Spitz and her associates (9) induced tumors with it in rats. While no bladder tumors occurred with these animals, proof of the carcinogenic activity of benzidine was definite.

### Analysis

Since benzidine is an aromatic amine it can be diazotized and coupled to form a colored substance. Sciarini and Mahew (10) have developed a rapid technique for estimating benzidine in industrial exposure which depends upon the oxidation of extracted benzidine by chloramine T to a color complex, which can then be estimated spectrophotometrically in the 2- to 10-microgram range with an accuracy of  $\pm 10$  per cent.

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## BENZOYL PEROXIDE

### Characteristics

Benzoyl peroxide, dibenzoyl peroxide,  $(C_6H_5CO)_2O_2$ , melting point  $104^\circ C$ ., exists as a white powder or as odorless rhombic crystals which deflagrate on heating and often explode spontaneously even at room temperature. It is insoluble in water but dissolves in acetone, benzene, toluene, ether, or acetic acid. Benzoyl peroxide is prepared by the action of sodium peroxide, barium peroxide, or hydrogen peroxide and sodium hydroxide on benzoyl chloride. When benzoyl peroxide dissolved in an organic solvent, such as ether or benzene, is treated with sodium ethoxide, benzoyl-sodium-hydrogen peroxide is formed. Sulfuric acid liberates perbenzoic acid,  $C_6H_5COOOH$ , melting point  $42$  to  $43^\circ C$ .

### Industrial Uses

Benzoyl peroxide is used as a bleaching agent for white flour and is called Lucidol (U. S. Patent 1,380,334), or when diluted with calcium phosphate it is called Novadelox (U. S. Patent 1,381,079). It is applied to flour as it is delivered to the bins by running a small stream into the regular stream of flour from a spout and there is no other mixing. Bleaching is accomplished within one day (1). Benzoyl peroxide is stated to have an accelerating effect on the activity of yeast. It is used as a bleaching agent for fats, oils, and waxes and is also used to polymerize monomeric acrylic esters. It is one of the most effective catalysts for bringing about copolymerization. In the manufacture of methyl methacrylate rods, the partially polymerized methyl methacrylate, containing about 10 per cent dibutyl or diamyl phthalate as a plasticizer and the requisite amount of benzoyl peroxide, is cast in tubes (2). Production of benzoyl peroxide in the United States amounted to 1,768,000 pounds in 1954.

### Toxicity

In spite of its somewhat extensive use in the flour-milling industry as a bleaching agent, very little investigation of the toxicity of benzoyl peroxide has been made and



so far no injurious effects of industrial importance have been noted. It is known, however, that benzoyl peroxide inhibits growth in plants by causing the disappearance of the food factor (3), and such feeding experiments as have been done with animals indicate that benzoyl peroxide causes loss of body weight and decreases the life span of the animals. According to de Vitéz, animals fed both flour paste and baked products made of flours treated with benzoyl peroxide have a deleterious effect on the health of the animal (4). While benzoyl peroxide is of relatively minor importance in industrial hygiene, the question has occasionally arisen regarding exposure of employees to small amounts of this material in environmental dusts. However, since benzoyl peroxide possesses a low order of toxicity, no particular danger has so far been indicated from this source. No maximum allowable concentration has been set by any agency for benzoyl peroxide dust.

### Analysis

The determination of benzoyl peroxide dust in air has been investigated by Dolin (5). The method advocated is based upon the oxidation of iodide by the peroxide and is stated to be sensitive to 3 micrograms by visual means, or to 1 microgram when read in a photoelectric colorimeter.

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## BENZYL CHLORIDE

### Characteristics

Benzyl chloride,  $\alpha$ -chlorotoluene,  $C_6H_5 \cdot CH_2 \cdot Cl$ , (not to be confused with *o*-chlorotoluene, which is 1-chloro-2-methyl-

benzene) is a colorless liquid with a pungent and somewhat unpleasant and irritating odor. Its melting point is  $-43^\circ C$ . and boiling point  $179^\circ C$ . ( $160^\circ$  at 92 millimeters). It is a very refractive liquid, having an index of refraction of  $n_{D^{15}} 1.5415$  and a density of  $D_{4/4} 1.1135$ . It is volatile with steam. Benzyl chloride is hydrolysed slowly by water and decomposes rapidly when heated in the presence of iron. Benzyl chloride is insoluble in water, but is readily soluble in alcohol, ether and in chloroform. It is a valuable reagent by means of which a number of derivatives may be prepared, as its chlorine atom is readily exchanged. When heated with water and lead nitrate it yields benzaldehyde. It is readily oxidized to benzoic acid. Benzyl chloride is prepared by the careful chlorination of boiling toluene.

### Uses

Benzyl chloride is extensively used in industry in the manufacture of basic and acid colors, pharmaceutical products, resins, synthetic tannins, and perfumes. It is used in the commercial preparation of both benzaldehyde and benzoic acid and finds particular application in the introduction of the benzyl group in intermediates prior to sulfonation in the preparation of acid dyes. The extent to which it is used is indicated by the production figures of 5,768,000 pounds in 1949 in the United States and 11,545,000 pounds in 1954.

### Toxicity

Aromatic compounds having a halogen-bearing side chain often have pronounced lachrymatory powers. Benzyl chloride is no exception to this. Its vapor is highly irritating to the eyes, nose, and throat and to all mucous membranes. It is classified as a powerful lacrimator. The paucity of information regarding industrial contact with this substance doubtless is the result of the unpleasant and rather immediate effects of exposure, and it therefore serves as its own warning agent. While the toxic dose of benzyl chloride vapor for undifferentiated cells was shown by Lallemand (1) to produce its effect in 5 hours, as compared with several days for such substances as the vapor of phenol, aniline, and carbon tetrachloride,

relatively large doses have been used in animal experiments without producing severe systemic poisoning. According to Sherwin and Hynes (2), both benzyl alcohol and benzaldehyde (which might conceivably be anticipated as hydrolytic and oxidative products and which are readily formed *in vivo*) are excreted as hippuric acid. Stekol (3) however found that the detoxication mechanism follows the path of mercapturic acid formation with elimination of the halogen and that the substance as finally excreted in the urine is benzylmercapturic acid. Stekol points out the interesting fact that benzyl chloride induces sensitization in animals and states that the tissue protein may be the common factor in the mechanism of sensitization and detoxication of benzyl chloride in animals. Flury and Zernik (4) state that 16 parts per million cannot be tolerated by man for longer than 1 minute. So far as industrial exposure is concerned, no maximum allowable concentration value has been established; however, 1 part per million has been suggested as a tentative figure. The possibility of sensitization with reference to workers exposed to low concentrations of benzyl chloride may be of particular interest and worthy of consideration in the establishment of a permissible working value.

### Analysis

Apparently no method for the determination of benzyl chloride as an aerial contaminant has been developed. However, the ease with which benzyl chloride is hydrolysed makes possible a convenient method of analysis of a collected sample by refluxing with a dilute aqueous solution of silver nitrate. Similarly it should also be possible to determine very small amounts by refluxing followed by a nephelometric procedure with a silver salt.

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## BITUMINOUS SUBSTANCES

### Characteristics

Asphaltum, mineral pitch, Judean pitch, bitumen, Trinidad asphalt, rock asphalt, Bermudez Lake asphalt, gilsonite, grahamite, and glance pitch all refer to natural asphalt. These various materials constitute only about 10 per cent of the total of asphalts consumed in the United States, while the petroleum asphalts account for at least 90 per cent of the asphaltic materials consumed in this country. The native asphalts are dark brown to black, solid or semi-solid hydrocarbons which usually are mixed with inorganic material such as limestone, clay, or, in the case of Trinidad asphalt, volcanic ash. The term *bitumen* is applied to the mixture of native or pyrogenous hydrocarbons, including various oxygen-, nitrogen-, and sulfur-bearing compounds, whereas the term *asphalt* is applied to the native or artificial product containing bitumen mixed with inert mineral matter. Bitumens are soluble in carbon disulfide. Coal tar and coal tar pitch both contain bitumen, but, while sharing many physical properties and commercial uses in common with asphaltic pitch and related substances, are not at all identical chemically with the latter. The former contain, or yield on distillation, a great variety of organic substances, such as benzene and more highly condensed aromatic compounds, including naphthalene, anthracene, and phenanthrene, together with phenols and heterocyclic compounds, such as thiophene, acridine, pyridine, quinoline, etc. Native asphalt on the other hand may be considered an end product from which the more volatile constituents have been removed. Both the natural and the artificial bitumens in carbon disulfide solution show a similar ultramicroscopic picture, but the natural and petroleum asphalts differ in this respect, owing to the mineral content of the former. The ultramicroscopic image of dilute solutions of coal tar in nitrobenzene, as well as similar solu-



tions of natural and petroleum bitumens, is that of carbon particles. The number of fine, freely moving particles is a measure of the binding power of the tar. When ether or ethyl acetate are added to a solution of asphaltic bitumen in carbon disulfide, precipitation of the so-called "asphaltenes" occurs. That portion of the bituminous substance soluble in carbon disulfide but insoluble in carbon tetrachloride is designated as the "carbenes". Grahamite and certain other hard native asphalts contain a certain amount of this fraction, while carbenes are absent from petroleum asphalt unless it has been overheated or overblown. The portion of material present in asphalt which is soluble in petroleum naphtha is designated as "petralenes" and represents the oily portion. The composition and physical properties of asphalt from various sources vary greatly and data with reference to specific gravity, melting point, asphaltene, resin and oil content, as well as penetration, ductility, and ash content have very little general significance, although in specific instances for purposes of comparison they are most important.

### Industrial Uses

It is unnecessary to elaborate on the multitudinous uses of asphalt, but it may be stated that these include the paving of streets, parking lots, and airports, as well as roofing of various types. Vast amounts of asphalt are also used in waterproofing structural elements of buildings, and for flooring, expansion joints in concrete, in the paint and varnish industry, in wood impregnation and electrical insulation, to mention but a few of its outstanding applications. The production of native asphalt and bitumens in the United States in 1951 amounted to 1,443,955 short tons, while the production of petroleum asphalt in 1951 amounted to 12,055,500 short tons (1). Coal tar produced in the United States in 1951 amounted to 795,311,283 gallons (1), an increase of 5,442,516 gallons over that of 1950.

### Toxicity

Workers are exposed to the dust of asphalt in crushing, grinding, and riddling

operations and to the fumes of this material in heating or boiling it, or, in special operations, such as the manufacture of steel where the molten metal is poured into pitch- or tar-coated molds (2). The grinding of asphalt which produces large quantities of dust has been said to cause serious affection of the cornea. Furthermore, the fumes arising from heated asphalt produce inflammatory conditions of the eyes and respiratory passages and a peculiar yellowish condition of the skin. Photosensitization is said to occur in individuals exposed to heated tar and this has been attributed to the acridine and anthracene content of the fumes. According to Flury and Zernik (3) not all asphaltic materials behave similarly. Thus, asphaltic residues from the distillation of American petroleum do not produce the effects attributed to other asphaltic materials. Tar melanosis occurs in workers after some weeks of exposure to coal tar fumes or vapor. The skin of employees so exposed first exhibits the yellowish pigmentation noted above. On further continued exposure the skin turns dark brown. The covered skin is not affected. Acne is common among tar workers exposed to the fumes of this material and the keratoses resulting from tar and pitch comedones occasionally results in a "shagreen" skin, according to White (4). The carcinogenic properties of coal tar and coal tar pitch have been a frequent matter of comment. Prior to 1942, according to Hueper (5), 130 cases of occupational cancer from this source had been reported in continental Europe since 1875, while 1,400 cases were reported in the British Isles since it was first observed in 1892. Davies (6) has referred to the intensely carcinogenic properties of certain coal tar derivatives, such as 3,4-benzpyrene and 1,2,5,6-dibenzanthracene.

While tar cancer has become a well-established entity, petroleum asphalt is stated to have a lower carcinogenic potency (7). It should be pointed out that certain constituents of coal tar fume, such as acridine (which is very irritating to the skin), are not carcinogenic. Hueper states: "Information as to the potential carcinogenic qualities of *native* asphalt is available only

in connection with the asphalt mined from the Pitch Lake in Trinidad. Ross, who cited the observations by physicians who were employed by the company handling the operations as Pitch Lake and who supervised the workers, stated that "no cutaneous epitheliomatous lesions had been seen in the workers engaged in the mining and transport of the asphalt." Thus, it would appear that the fumes or dust of native asphalts do not present a substantial health hazard in comparison with fumes or dust of coal tar or coal tar pitch.

### Analysis

The chemical and physical examination of asphaltic or other bituminous material, while of great industrial importance, is of little concern to the industrial hygienist, except in those few cases where identification of the material may be in doubt. On the other hand, the dust or fume content of the air may be of significance. There is no convenient method available for the identification of tar, pitch, or asphaltic fumes in general. However certain constituent substances, particularly in the case of tar fumes, are useful for purposes of identification. Thus, the diazo reaction for fumes carrying phenols, the anthraquinone reaction for anthracene, and the thiocyanate test with various metal salts for acridine may be found helpful in such instances. In the case of dust exposures, samples may be secured in an impinger apparatus using water as the suspension medium and dust counts and particle size measurements may be made in the usual manner. With material somewhat oily in nature, it may be necessary to suspend the particulate material in alcohol rather than water, in order to secure adequate dispersion for microscopic observation.

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## BROMOFORM

### Characteristics

Bromoform, tribromomethane,  $\text{CHBr}_3$ , is a heavy, colorless liquid, with a characteristic odor and taste somewhat reminiscent of that of chloroform. It boils at  $149.6^\circ \text{C}$ ., melts at  $7.8^\circ \text{C}$ ., has a density of 2.980, and index of refraction  $n_D^{20}$  of 1.5980. The vapor pressure at  $22^\circ \text{C}$ . is 5 millimeters of mercury; and at  $48^\circ \text{C}$ . it is 20 millimeters of mercury. Bromoform is soluble in the usual organic solvents and dissolves in water to the extent of 3.19 grams per liter at  $30^\circ \text{C}$ . Bromoform is prepared by heating acetone or ethyl alcohol with bromine in the presence of alkali followed by distillation.

### Industrial Uses

While bromoform has been employed medicinally to a slight extent as an antispasmodic, its toxicity has largely contraindicated this practice. Apart from its application to organic synthesis, bromoform is largely used by petroleum geologists for the separation of mineral species in sedimentary petrographical surveys.

### Toxicity

Bromoform has anesthetic properties similar to those of chloroform but is not sufficiently volatile for inhalation purposes and is far too toxic to be recommended. In addition to its narcotic effects, it is a liver and metabolic poison in general. The inhalation of small amounts of bromoform vapor causes irritation, provoking the flow of tears and saliva and reddening of the face. According to Gonzales and his associates (1), a number of deaths have been caused by the use of bromoform as a sedative in whooping cough. In contrast with this, severe industrial poisoning by the inhalation of bromoform has not so far been reported. It should



be pointed out, however, that petroleum geologists working in closed rooms with a large number of funnels or open separatory flasks as required for routine procedure in the separation of minerals can be subjected to appreciable concentrations of bromoform as an atmospheric contaminant. No threshold limit value has so far been established for bromoform.

### Analysis

The determination of small concentrations of bromoform vapor in air should present no particular difficulty to the industrial hygiene chemist. In addition to the general methods for the determination of the halogens in halogenated hydrocarbons, bromoform may be decomposed by a microcombustion method and the inorganic or the free bromine caused to react with fluorescein (2). The latter reacts with free bromine to form eosin and the depth of coloration is proportional to the amount of bromine present.

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## 1,3-BUTADIENE

### Characteristics

1,3-Butadiene,  $\text{CH}_2=\text{CH}-\text{CH}=\text{CH}_2$ , an unsaturated hydrocarbon, is a colorless gas at room temperature and has an aromatic odor. It boils at  $-4.7^\circ\text{C}$ . under 1 atmosphere pressure. The specific gravity is 0.6274  $\text{r}$  60/60 (1) and the melting point is  $-108.9^\circ\text{C}$ . Butadiene is insoluble in water but infinitely soluble in a number of organic solvents. This substance is manufactured in quantity by a number of different methods. The earlier process of catalytic conversion of ethyl alcohol into butadiene has been gradually surpassed by its derivation from cracking naphtha and light oil. Another process which has, however, not reached any particular commercial magnitude is that of the dehydration of 2,3-butylene glycol made by the fermentation of grain.

### Industrial Uses

The great importance of butadiene in the production of synthetic rubber, following the sudden termination of the importation of natural rubber at the beginning of the war, is shown by its production figures. The total production of butadiene during 1946 was 1,074,040,000 pounds of which 780,000,000 pounds was derived from petroleum, while the remainder was prepared from ethanol. Production of butadiene from alcohol decreased from 723,814,000 pounds in 1944 to 470,000,000 pounds in 1946, due largely to increased production from petroleum (2). In 1946, 1,707,784,000 pounds of synthetic rubber was produced in the United States and of this 1,377,517,000 pounds was Buna S (the butadiene-styrene type of synthetic rubber) and 13,615,000 pounds was Neoprene and Buna N (the butadiene-acrylonitrile type) (3).

### Toxicity

The toxic effects of 1,3-butadiene were extensively investigated by Carpenter and his associates (4) and, in general, it may be said that its toxicity to man is not very great. Butadiene in concentrations of 600, 2,300, and 6,700 parts per million caused no significant progressive injury to small animals during an 8-month exposure period of 6 days a week,  $7\frac{1}{2}$  hours a day. However, the highest concentration did retard growth slightly and in some instances caused light, cloudy swelling of the liver. The narcotic action of butadiene was shown to be less than that of benzene or toluene. Two human subjects found that 8,000 parts per million of butadiene had an effect no greater than 200 parts per million of toluene. Apart from its narcotic effect at very high concentrations, butadiene is regarded as practically innocuous and has little, if any, cumulative effect.

### Analysis

The method employed by Carpenter and his associates (4), which is applicable to the determination of butadiene in the absence of other organic gases, depends upon the oxidation of the butadiene with iodine pentoxide and determination of the liberated iodine. In the presence of other saturated

and unsaturated hydrocarbons, Cuneo and Switzer (5) have developed a method which consists essentially in absorption of the gas by mercuric nitrate solution and subsequent hydrogenation. Gregg (6) has recently modified the conventional molten maleic anhydride procedure for the technical determination of butadiene by devising an especial absorption pipette.

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## 2-BUTANONE

### Characteristics

2-Butanone, methyl ethyl ketone,  $\text{CH}_3\text{CH}_2\text{COCH}_3$ , boils at  $80^\circ\text{C}$ ., melts at  $-86.4^\circ\text{C}$ ., has a density of  $d_{20/4}$  0.805, and an index of refraction of  $n_{20/D}$  1.3791. It is a colorless liquid with an odor resembling that of acetone and is miscible with water, alcohol, and ether. With a saturated solution of sodium bisulfite, 2-butanone forms a bisulfite addition compound and on oxidation with chromic acid, it yields acetic acid. It has a vapor pressure of approximately 119 millimeters of mercury at  $30^\circ\text{C}$ . The flammable point for butanone is reached when the concentration rises above 1.81 per cent at room temperature. At initial temperatures of 100, 150, and  $200^\circ\text{C}$ ., the lower flammable limits of 2-butanone in air are 1.7, 1.5, and 1.3 per cent by volume and the upper limits are 9.7, 9.8, and 9.9 per cent respectively (1). Methyl ethyl ketone may be prepared by the reaction of 2-chloro-2-butane with slightly diluted sulfuric acid at

20 to  $40^\circ\text{C}$ . followed by steam distillation (2).

### Industrial Uses

Methyl ethyl ketone is a valuable solvent for vinyl resins, nitrocellulose, and synthetic rubber. In the anhydrous state, it presents solvent properties equal to that of acetone, its evaporation rate, however, is definitely slower than acetone, a fact responsible for its initial bluish-resistance in lacquer. There is a tendency to replace ethyl and isopropyl acetate, as well as benzene, with butanone. Butanone is an active solvent and is used in thinners for wood-finishing lacquers, as a solvent in cellulose acetate lacquers, and as a solvent for resins used to waterproof military raincoats. It is used in organic synthesis, in paint removers, in artificial leather dressings, in dopes and dyes, and in the manufacture of smokeless powder.

### Toxicity

Patty, Schrenk, and Yant (3) found that butanone vapor is markedly irritating to the nose and eyes of man in concentrations found to be harmful to guinea pigs. Furthermore, the vapor has distinct warning properties of both odor and irritation in those concentrations which were apparently harmless to guinea pigs after several hours of exposure. The symptoms of intoxication, in general, are those of eye and nose irritation and, in particular, narcosis. Flammable mixtures of butanone vapor in air are practically intolerable because of these irritant properties. Specht, *et al.* (4) found that with guinea pigs, butanone produced a progressive narcosis characterized by depression of body temperatures, respiratory rate, and heart rate in direct proportion to the concentration of the inhaled vapor. Greenburg and Moskowitz (5), in an investigation of solvents in the synthetic rubber industry, found that as a solvent for Buna N, methyl ethyl ketone could be tolerated in higher concentrations than either ethylene dichloride or propylene dichloride and that employees should experience no difficulty in working in concentrations as high as 500 parts per million. Since butanone is often substituted for benzene as an effective sol-



vent for gums and resins and as a latent solvent for cellulose acetate, it should be pointed out that disabling skin dermatoses may develop in sensitive individuals exposed to this material (6). While a sensory response of 200 parts per million has been suggested (7), the maximum allowable concentration values adopted by various official industrial hygiene agencies vary from 150 to 500 parts per million.

### Analysis

Cassar's method (8) has been used with minor modifications in several investigations relating to the toxicity of butanone. In this method, butanone reacts with iodine in alkaline solution and the excess iodine is titrated with standard sodium thiosulfate solution. In using this method for the determination of quantities of butanone varying from 16 to 48 milligrams, Patty, Schrenk, and Yant (3) obtained an average recovery of 107 per cent. The increase is apparently due to a secondary reaction in which 10 mols of iodine react with 1 mol of butane in place of 6 mols of iodine with 1 mol of ketone. As the results are consistent, however, the method is useful over the range indicated.

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## *n*-BUTYL ACETATE

### Characteristics

*n*-Butyl acetate,  $\text{CH}_3\text{CO}_2\text{C}_4\text{H}_9$ , is a colorless liquid with an agreeable odor in low concentrations, but disagreeable in concentrated form. The boiling point and density of purified *n*-butyl acetate are 126.09° C. and  $d_{25/4}$  0.87636 (1). The index of refraction is  $n_{15/D}$  1.39614 and the flash point is 39° C. The vapor pressure of *n*-butyl acetate is 3.0 millimeters of mercury at 0° C., 15.0 millimeters of mercury at 25° C., and 45.0 millimeters of mercury at 50° C. *n*-Butyl acetate is miscible in all proportions with the common organic solvents. The saponification equivalent is 116. On saponification with alkali, *n*-butyl acetate yields *n*-butyl alcohol and acetic acid. *n*-Butyl acetate is made from *n*-butanol which is produced abundantly and cheaply by the Weizmann fermentation process, using the organism *Clostridium acetobutylicum* Weizmann, which is capable of fermenting a variety of starches. The fermentation products are butanol, acetone, and ethanol in the ratio of 6:3:1. Optimum fermentation occurs within the range 37 to 42° C. and a pH of 5 to 7. About 96 per cent of the original amount of carbohydrate is converted to fermentation products.

### Industrial Uses

*n*-Butyl acetate is largely used in the lacquer industry as an important solvent for nitrocellulose lacquers. It is also used in the manufacture of lacquer inks, coated papers, patent and enameled leathers, photographic film, polishes, pyroxylin plastics, and in the manufacture of vinyl resin and cellulose acetopropionate finishes. During 1954, the United States production of normal butyl acetate was 78,255,000 pounds. *n*-Butyl acetate is especially suitable as a solvent for nitrocellulose in the lacquer industry because of its slow evaporation property. Lacquer produced with this solvent has good "blush resistance" and good flow. While such

solutions made with highly nitrated cotton are viscous, it has been found that pyroxylin can be modified by heating under pressure in contact with very dilute acid. Solutions of this material in *n*-butyl acetate can be made of adequate concentration, yet are thin enough to flow freely. The volume of *n*-butyl acetate consumed by the lacquer industry is probably several times that of all the other solvents in this class.

### Toxicity

The acute physiological response of guinea pigs to air containing a commercial grade of normal butyl acetate was determined by Sayers, Schrenk, and Patty (2). At room temperature it was not possible to attain a concentration that was dangerous to the life of guinea pigs in 30 to 60 minutes. Exposure to 10,000 to 14,000 parts per million per cent vapor is considered dangerous to life of guinea pigs after several hours; 7,000 parts per million per cent is the maximum amount for 1 hour exposure without serious disturbance other than eye and nasal irritation; and 3,300 parts per million per cent is the maximum amount for several hours' exposure with but slight or no symptoms. The symptoms are principally those of eye and nasal irritation and narcosis. Men exposed to the above percentages of *n*-butyl acetate vapor in air even for a short time pronounced the atmosphere extremely disagreeable because of its strong odor and irritation to eyes and nasal passages (2). Similar effects on workers with butyl acetate have been observed by Busing (3) and by Baldi (4).

### Analysis

Determination of normal butyl acetate in air when present as the only constituent of exposure may be made by adsorption on known weights of activated charcoal. Since, however, the solvent vapor is usually made of several constituents, this method is only applicable in restricted cases. An alternative method consists in hydrolysis of a sample of the contaminated air which should be from 5 to 20 liters in volume. Such a sample drawn through a bottle of this volume until uniform conditions exist is absorbed by ad-

mitting 10 to 50 milliliters of 95 per cent alcohol and the solution washed into an Erlenmeyer flask with additional alcohol. An accurately measured volume of tenth normal sodium hydroxide is then added and the solution refluxed for 1/2 hour in order to hydrolyze the acetate. The excess sodium hydroxide is then titrated with standardized tenth normal sulfuric acid using phenolphthalein as an indicator and the quantity of *n*-butyl acetate calculated from the amount of sodium hydroxide required for hydrolysis.

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## THE BUTYL ALCOHOLS

### Characteristics

Four isomers of butyl alcohol,  $C_4H_{10}O$ , are theoretically possible—two primary, one secondary, and one tertiary. For convenience, their properties are listed in Table 2.

Normal butyl alcohol is a colorless liquid which at room temperature dissolves in 11 parts of water. The flash point is 34° C., the rate of evaporation from filter paper is about 1/300 that of ether, and the vapor pressure at 20° C. is 4.3 millimeters of mercury and at 40° C. is 18.6 millimeters of mercury. *iso*-Butyl alcohol is also a colorless liquid and it dissolves in about 10 parts of water. It has a flash point of 22° C. and a volatility of 1/500 that of ether. While only slightly soluble in water as indicated above, all the butyl alcohols dissolve freely in the usual organic solvents. Normal butyl alcohol is largely obtained by the bacterial action of selected organisms on corn and other carbohydrate-bearing substances. Several types of bacteria



TABLE 2

Substance	Formula	Density d 20/4	Boiling Point °C.	Melting Point °C.	Index of Refraction n 25/D
<i>n</i> -Butyl alcohol, (butanol-1)	$C_2H_5-CH_2-CH_2OH$	0.80960	118.0	-90.2	1.3974
<i>iso</i> Butyl alcohol, (2 methyl-propanol-1)	$(CH_3)_2-CH-CH_2OH$	0.80196	108.1	-108.0	1.3939
Secondary butyl alcohol, (butanol-2)	$C_2H_5-CHOH-CH_3$	0.80692	99.5	-114.7	1.39495
Tertiary butyl alcohol, (2 methyl-propanol-2)	$(CH_3)_3COH$	0.78670	82.5	25.55	1.38779 n 20/D

are used, such as *Bacillus macerans*, the butylic bacillus of Fitz, or the organism known as *B. clostridium acetobutylicum* which is used in the widely employed Weizmann process. Secondary butyl alcohol is prepared synthetically from the vapor pressure cracking of gas containing butene-1 and butene-2. *iso*Butyl alcohol has been obtained in large quantities as a by-product in the preparation of synthetic methyl alcohol. It exhibits the typical reactions of a primary alcohol except that the presence of a branched chain next to the carbinol group makes rearrangement unusually easy. Secondary butyl alcohol is produced by hydrating the corresponding olefin. Tertiary butyl alcohol is readily obtained from the hydration of isobutylene.

### Industrial Uses

Of the 408,061,000 pounds of butyl alcohol (including all isomers) manufactured in 1954, 194,407,000 pounds was normal butyl alcohol. Approximately 60 per cent of the total amount is used in the manufacture of chemicals of which the most important are butyl acetate, butyl phthalate, butyl cello-solves, and butyl amines. Fifteen per cent of the total amount manufactured was used in lacquer solvent material for various types of coatings (aircraft and ammunition), textiles, dyes, and leather. Additional uses for the butyl alcohols are to be found in the field of resins and plastics, photography and films, hydraulic brake fluids, and oil additives. A particularly useful application of butanol in industry is that of blending otherwise incom-

patible materials. For example, about 5 per cent of butanol will permit petroleum naphtha and alcohol to blend in all proportions. Solutions of certain resins and gums, which cannot be mixed together without precipitation of one of the dissolved constituents, yield a perfectly homogeneous solution with the aid of butanol. The commercial value of isobutyl alcohol is less than that of normal butyl alcohol but greater than that of secondary butyl alcohol. It is used as a lacquer co-solvent but particularly for the production of the corresponding acetate. Secondary butyl alcohol is important as an intermediate in the production of secondary butyl acetate and of butanone. Tertiary butyl alcohol is employed as an alkylating agent in the preparation of tertiary butylphenol.

### Toxicity

Although a considerable amount of animal experimentation has been done with reference to the physiological response to *n*-butyl alcohol and its isomers, no serious industrial poisoning has been traced specifically to any one of these substances. *n*-Butyl alcohol in a single dose is approximately three times as toxic as ethyl alcohol and the vapor is more irritating than that of ethyl alcohol but less than that of amyl alcohol. Recent experimental work, however, in which the toxicities of a number of alcohols were compared with reference to their effects on goldfish, indicates that the toxicity of normal butyl alcohol is higher than previously reported (1). Furthermore, Cogan and Grant (2) have reported an unusual type of

keratitis associated with industrial exposure to *n*-butanol, although they were unable to reproduce these effects in mice, guinea pigs, rabbits, or dogs. Tabershaw, Fahy, and Skinner (3), in an investigation of six industrial plants using butanol as a solvent, found that eye inflammation occurs when the atmospheric concentration of butanol vapor is above 50 parts per million. Smyth and Smyth (4) found that animals survived exposure to 100 parts per million over a long period of time but showed a definite change in the blood picture. These experiments revealed a decrease in erythrocytes and a relative and absolute lymphocytosis. While experimental work has confirmed Overton's early statement that the normal alcohols are always more toxic than their secondary isomers, the differences noted with the butyl alcohols are not striking and the question of the relative toxicity of the various butyl alcohols is largely academic. Nelson and his co-workers (5) have suggested a sensory limit of less than 25 parts per million, since many individuals find the odor of butanol in concentrations above that figure to be disagreeable. Various governmental agencies have set a maximum allowable concentration at values varying from this figure to 300 parts per million.

### Analysis

*n*-Butanol yields *n*-butyraldehyde on oxidation with chromic and sulfuric acids, whereas isobutyl alcohol under similar conditions yields isobutyraldehyde, boiling point 63° C. and isobutyl isobutyrate, boiling point 148.7° C. Tertiary butyl alcohol, when similarly oxidized, yields acetone, acetic acid, and carbon dioxide. Distilled with hydrobromic acid, *n*-butyl alcohol yields *n*-butyl bromide, boiling point 101° C.; secondary butyl alcohol yields secondary butyl bromide, boiling point 91° C.; isobutyl alcohol yields isobutyl bromide, boiling point 91° C.; and tertiary butyl alcohol yields tertiary butyl bromide, boiling point 72° C. (The melting points of the lower alcohols are rather low but are useful in the differentiation of tertiary butyl alcohol.) The xanthogenate test referred to by Feigl (6) is said

to be sensitive to 1 milligram, but is not specific for the butyl alcohols. Similarly, the iodimetric titration method of determination is not specific, since other substances respond similarly. The differentiation of the various butyl alcohols by their color reaction with furfural has been investigated by Ekkert (7) and the color development presents the possibility of quantitative application.

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## BUTYLAMINE

### Characteristics

The physical properties of the butylamines are listed in Table 3. *n*-Butylamine, or 1-aminobutane, is the butylamine of most industrial importance, although the other amino derivatives of butane are commercially available. *n*-Butylamine is a liquid with an ammoniacal odor. It is miscible with water, alcohol, and ether.

### Uses

*n*-Butylamine is an intermediate for the manufacture of pharmaceuticals and dye-stuffs and is used in certain synthetic tan-



TABLE 3

Substance	Boiling Point °C.	Melting Point °C.	Density	Index of Refraction
<i>n</i> -Butylamine.....	78	-50	D <sub>15</sub> 0.742	n <sub>20/D</sub> 1.401
<i>sec</i> -Butylamine.....	63	-104	D <sub>20</sub> 0.724	n <sub>20/D</sub> 1.394
<i>iso</i> -Butylamine.....	68-9	-85	D <sub>20/20</sub> 0.732	n <sub>17/D</sub> 1.3988
<i>tert</i> -Butylamine.....	45	-67.5	D <sub>15</sub> 0.700	n <sub>18/D</sub> 1.3794

ning materials. Production in the United States in 1953 amounted to 274,000 pounds.

### Toxicity

*n*-Butylamine is an irritant substance to the skin on contact with the liquid and is irritating to the respiratory tract on inhalation of the vapor. Hanzlik (1) found that it caused pulmonary edema and also affected the central nervous system, acting at first to cause stimulation, and finally depression, convulsions and narcosis. Smyth (2) reports the survival of rats following an exposure for 4 hours at 2,000 parts per million of butylamine, but die following exposure to 4,000 parts per million. Injury to the skin and cornea from the liquid is severe. The most important effect of butylamine inhalation, according to Smyth, is respiratory tract irritation, with lung edema as the maximum injury. Levels above 5 parts per million for workers with an 8-hour daily exposure tend to be irritating (3).

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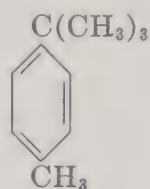
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## 1-*tert*-BUTYL-4-METHYLBENZENE

### Characteristics

1-*tert*-Butyl-4-Methylbenzene, *p*-*tert*-butyltoluene, is a liquid boiling at 192.76° C. at 760 millimeters and freezing at -52.515° C. Its density is D<sub>25/4</sub> 0.8573 and its index of refraction is n<sub>20/D</sub> 1.4948. It has a molec-

ular weight of 148.238 and it has the following structural formula



### Toxicity

Hine and his associates (1) classify *p*-*tert*-butyltoluene as slightly toxic on ingestion, moderately toxic on inhalation, and practically nontoxic on skin contact. The LD<sub>50</sub> value for oral ingestion by rats was found to be about 1,543 milligrams per kilogram of body weight. This substance produces depression of the central nervous system and irritation of the pulmonary tract as its chief toxic inhalation effect with animals, while repeated exposures cause liver and kidney changes. Its effect on the blood more nearly resembles that of benzene rather than toluene, but in this it is not constant, nor as severe as with benzene. Men exposed to the vapor readily recognized concentrations as low as 5 parts per million, but the vapor was not especially unpleasant at 80 parts per million. With some individuals engaged in pilot plant production of *p*-*tert*-butyltoluene a low-grade, transient intoxicating effect was noted and the symptoms were chiefly referable to the cardiovascular, hematopoietic, and central nervous systems. A safe maximum allowable concentration of 10 parts per million was recommended for *p*-*tert*-butyltoluene.

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## isoBUTYL METHYL KETONE

### Characteristics

*iso*Butyl methyl ketone, hexone,  $(\text{CH}_3)_3\text{CHCH}_2\text{COCH}_3$ , is a colorless, stable liquid with a pleasant, somewhat camphoraceous odor. Its boiling point is  $116.8^\circ\text{C}$ ., freezing point  $-84.7^\circ\text{C}$ ., density  $d_{20/4}$  0.8008, and index of refraction  $n_{17/D}$  1.39694. While it is insoluble in water, it is miscible with alcohol, ether, benzene, and, in fact, most organic solvents. The vapor pressure of this substance is 15.7 millimeters of mercury at  $20^\circ\text{C}$ . and its flash point is  $24^\circ\text{C}$ . *iso*Butyl methyl ketone yields a sulfite addition compound when treated with a saturated aqueous solution of acid sodium sulfite. When oxidized with chromic acid, it yields *isobutyric*, *isovaleric*, and acetic acids. When reduced with sodium and moist ether, it yields *isobutyl methyl carbinol*,  $(\text{CH}_3)_2\text{CH}\cdot\text{CH}_2\cdot\text{CH}(\text{OH})\text{CH}_3$ .

### Industrial Uses

In common with many of the ketones, *iso*-butyl methyl ketone is a solvent for nitrocellulose and certain types of cellulose ethers. It is also used commercially as a solvent for various oils, fats, waxes, natural and synthetic gums and resins. Although *isobutyl methyl ketone* evaporates about 50 per cent faster than butyl acetate, it is used to some extent in solvent mixtures for lacquers. In general, however, it is inferior to butyl acetate with respect to its solvent properties and the stronger odor of the commercial product somewhat limits its use.

### Toxicity

The inhalation of *isobutyl methyl ketone* vapor causes irritation of the conjunctival and nasal mucosa in man at concentrations below 0.1 volume per cent according to Specht (1, 2) and this indicates good warning qualities. At higher concentrations, marked irritation is evident in guinea pigs exposed to this vapor as is evidenced by lacrimation and salivation. Progressive narcosis occurs and death finally ensues at one volume per cent in about four hours exposure period. Complete recovery can be effected, however, by removal at any but the

terminal stages. The narcosis produced by inhalation of *isobutyl methyl ketone* vapor is characterized by depression of body temperature, the respiratory rate, and the heart rate, as well as by the abolition of corneal, auditory, and equilibratory reflexes. Gross and microscopic pathology is slight and resembles that of most acute reactions to solvent exposures. According to Henderson and Haggard (3), the irritant action of *isobutyl methyl ketone* is more marked in relation to its anesthetic effect than is the case with acetone.

### Analysis

The determination of *isobutyl methyl ketone* as an aerial contaminant may be made by the method of Patty, Schrenk, and Yant (4) as modified by Specht (1). This procedure, which is an iodine titration method, gave apparent recoveries of 104 per cent and is satisfactory for the concentration determined by this investigator.

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## n-BUTYL METHYL KETONE

### Characteristics

*n*-Butyl methyl ketone, hexanone-2,  $\text{C}_4\text{H}_9\cdot\text{CO}\cdot\text{CH}_3$ , is a water-clear liquid with an odor resembling acetone, although somewhat more pungent. The boiling point of this substance is  $127.8^\circ\text{C}$ ., its density  $d_{20/4}$  is 0.81127, and its index of refraction  $n_{20/D}$  is 1.40069. *n*-Butyl methyl ketone is but slightly soluble in water, although readily soluble in a variety of organic solvents.



### Industrial Uses

In common with many of the ketones, *n*-butyl methyl ketone is a good solvent for nitrocellulose. As an organic solvent, it is used to some extent for oils, fats, and waxes, and for vinylite products. It is used in the manufacture of lacquers and also in varnish and lacquer removers.

### Toxicity

The physiological response of animals exposed to the vapor of *n*-butyl methyl ketone was determined by Schrenk and his associates (1). Using guinea pigs as experimental animals, these investigators found that a concentration of 1 to 2 volumes per cent in air killed the animals in a few minutes, while the maximum amount that could be endured for 60 minutes without serious disturbance was 0.3 volume per cent. The latter concentration was found to be very irritating to human beings, however. The maximum concentration that could be tolerated by animals for several hours with but slight or no symptoms was 0.1 volume per cent. At this concentration, moderate eye and nasal irritation occurs in human beings. Death apparently occurs due to a state of narcosis rather than to lung irritation. In some instances, animals were unconscious for several hours following exposure but appeared normal 24 hours after exposure. Specht and his associates (2) found that the progressive general narcosis was characterized by depression of the body temperature, the respiratory rate, and the heart rate, as well as the abolition of corneal, auditory, and equilibratory reflexes. The depressant action of this ketone is greater than that of acetone, methyl ethyl ketone, or methyl propyl ketone and the incidence of onset of irritation, weakness, coma, and death was shown to occur earlier. The vapor of this ketone is immediately irritating even at 0.12 volume per cent.

### Analysis

The method of analysis adopted for the determination of the concentration of this ketone in air is the iodine titration procedure. Results obtained by this method are apparently satisfactory over ranges varying

from 2 to 0.1 per cent by volume, although somewhat higher apparent recoveries are obtained at lower concentrations (2).

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## CARBON DIOXIDE

### Characteristics

Carbon dioxide,  $\text{CO}_2$ , is a colorless, odorless gas with a sharp taste. The density of the gas under standard conditions (air = 1) is 1.52909. One liter at 0° temperature and 760 millimeters of pressure weighs 1.9678 grams. Carbon dioxide gas is readily liquefied and when a quantity of the liquid is allowed to evaporate quickly, the heat of vaporization is withdrawn from the remaining liquid which consequently freezes to a snow-like mass which is now marketed as "dry ice". At atmospheric temperature, water dissolves about its own volume of carbon dioxide forming carbonic acid. One volume dissolves in 0.6 volume of water at 0° C. or 1 gram in 300 milliliters of water at this temperature. Carbon dioxide is less soluble in alcohol or most other organic solvents than in water. The aqueous solution is feebly acidic and when boiled is completely decomposed with the escape of carbon dioxide.

### Industrial Uses

The industrial utilization of carbon dioxide has grown enormously during recent years. The production of gas or liquid increased from 153,575,000 pounds in 1931 to 217,266,000 pounds in 1946, while the production of solid carbon dioxide (dry ice) increased from 84,954,000 pounds in 1931 to 644,592,000 pounds in 1946 (1). The total output of gas, liquid and solid  $\text{CO}_2$ , had increased to 743,368 short tons in 1953. Carbon dioxide gas is used in the Solvay process (soda ash and bicarbonate manufacture)

and as an autoxidant; the liquid form is principally used in the beverage industry, as a fire extinguishing agent, and as blasting material in the "soft" explosion method for coal mining. Solid carbon dioxide is used as a refrigerating agent and for shrink-fitting metal parts in industry.

### Toxicity

Carbon dioxide is a natural excretory product of the body and is not a toxic substance in the usual sense. It is true that in quantity it has a weak, irritating action and in baths charged with carbonic acid a slight reddening of the skin has been noted and some irritation and prickling of denuded surfaces is produced. Some irritation of the respiratory passages follows the inhalation of a high concentration. The most outstanding effect of inhalation is the increase in ventilation produced by stimulation of the respiratory center. The recent investigations of Schaefer (2) on fleet type submarines with an exposure to 3 per cent carbon dioxide and 15 to 17 per cent oxygen indicate a variation in effect with duration of exposure. In contrast with experiments of short duration in which addition of carbon dioxide has a beneficial effect in alleviating symptoms of oxygen lack, such an addition of carbon dioxide has an impairing effect under conditions of exposure over days and weeks. Death from carbon dioxide poisoning is not preceded by convulsions. In one sense, carbon dioxide acts somewhat as a protoplasmic poison since cellular combustion is decreased to an extraordinary extent as shown by the greatly decreased oxygen absorption. Numerous accidents involving carbon dioxide have been reported in the literature. Such accidents have occurred in cleaning of wells (3); in ship holds (4, 5); in silos (6, 7); and in vaults or cellars (8).

### Analysis

Various methods have been suggested for the determination of small amounts of carbon dioxide, such as the absorption of this gas by barium hydroxide followed by microtitration, or its absorption in sodium bicarbonate solution to the point of saturation with measurement of the resulting hydrogen

ion concentration. Colorimetric comparison can be made with a series of pH standards. Traces of carbon dioxide may also be determined by the decrease in intensity of color of a dilute solution of carbon dioxide colored with phenolphthalein through which the air is passed. Spector and Dodge (9) have established the accuracy of this method as equivalent to 10 per cent in the analysis of carbon dioxide in a liter sample of air containing 0.001 per cent of carbon dioxide. Various mechanical devices are commercially obtainable for the continuous registration of carbon dioxide in such material as flue gases, where a check on efficiency of combustion is important.

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## CARBON DISULFIDE

### Characteristics

Carbon disulfide,  $\text{CS}_2$ , is a colorless refractive liquid, molecular weight 76.13, specific gravity 1.263 at  $20^\circ/4^\circ \text{C.}$ , melting point  $-112^\circ \text{C.}$ , and boiling point  $46.2^\circ \text{C.}$  It has an unpleasant characteristic odor, is soluble in 100 parts of water to the extent of 0.14 parts at  $49^\circ \text{C.}$ , and mixes freely with alcohol and ether. It is a good solvent for rubber, fats, and oils. Its flash point is  $-25.5^\circ \text{C.}$  to  $-20^\circ \text{C.}$  and it has an ex-



tremely low ignition temperature of 120° to 156° C. It is endothermic and the vapor may be ignited by a heavy blow. Since the vapors are heavier than air, the vapor density being 2.62 (air = 1), it may travel a considerable distance to a source of ignition and flash back. The vapor pressure of carbon disulfide is 127.0 millimeters of mercury at 0° C., 294.3 millimeters at 19.7° C., and 760.0 millimeters of mercury pressure at 46.2° C. Carbon disulfide may be prepared by passing sulfur vapor over red hot carbon and is commercially prepared in carbon-arc electric furnaces from coke and sulfur.

### Industrial Uses

Carbon disulfide is used in the manufacture of viscose rayon, chemicals, and rubber. It is used as an insecticide, a solvent for fats, oils, and phosphorus, a preservative, and it is used to some extent in varnishes and enamels. It occurs as a by-product in the manufacture of coal gas, in the distillation of tar, and in the manufacture of certain chemicals. During 1954, production in the United States amounted to 476,503,000 pounds.

### Toxicity

Carbon disulfide has a pronounced narcotic action with high concentrations of vapor. Reddening of the face occurs, euphoria followed by stupor, motor restlessness, occasionally cramps, unconsciousness, and possibly death, due to paralysis of the respiratory center. If recovery occurs, the well-known after effects of narcosis are apparent and epileptiform cramps and sight disturbances can continue for a long time. A variety of symptoms occur following repeated inhalation and these toxic symptoms in order of occurrence are: nervousness, irritability, indigestion, bizarre dreams leading to insomnia, excessive fatigue, loss of appetite, and headache. The signs of poisoning generally noted include a waxy pallor, low blood pressure, and extreme excitement or depression. Repeated exposures to low concentrations resulting in physical disturbances may also occur. A concentration of about 480 parts per million represents the maximum amount that can be inhaled for

1 hour without serious disturbance. In industry, absorption of carbon disulfide occurs mainly through the lungs, although toxic quantities may be absorbed through the skin. Absorbed carbon disulfide is largely excreted through the lungs, but a small fraction appears to be excreted through the urine, the sweat, and feces (1). The urinary excretion of carbon disulfide has been used as an index of absorption. Suitable respiratory protection is needed if even small concentrations of carbon disulfide vapor are to be encountered.

According to Fabre *et al.* (2) the physiological action of carbon disulfide appears to be irreversible. Vigliani and Cazzulla (3) found that workers under 45 years of age who had been exposed to a working atmosphere containing 0.1 to 1 milligram CS<sub>2</sub> per liter for about 20 years developed asthenia, progressive impairment of gait and mental deterioration. Cesaro (4) has developed criteria for the diagnosis of occupational carbon disulfide poisoning. Brieger (5) has studied the effects of high concentrations of carbon disulfide vapor on the heart in several series of animal experiments. The electrocardiograms showed only minor differences normal in unexposed animals. Furthermore, histological examination of the heart revealed no significant changes.

### Analysis

Carbon disulfide is chiefly of interest to the industrial toxicologist as an aerial contaminant, and various methods have been proposed for the determination of amounts of carbon disulfide in the air of workrooms. The most satisfactory method for this purpose depends upon the formation of copper diethyldithiocarbamate and its colorimetric evaluation. A known volume of air containing carbon disulfide is bubbled through absolute alcohol or isobutanol to which diethylamine and copper acetate are added to form copper diethyldithiocarbamate (6). With the photometric procedure, it is possible to detect concentrations as low as 1 part per million. A modification of this method has been proposed for the determination of carbon disulfide in the blood and urine of workers exposed to this substance

(7). Sonnenschein and Schafer (8) have developed a method for the simultaneous determination of small amounts of hydrogen sulfide and carbon disulfide in the atmosphere. The former is based on the conversion of *p*-phenylaminodimethyldiamine sulfate to methylene blue, while the carbon disulfide is determined by a modification of the diethylthiocarbamate reaction.

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## CARBON MONOXIDE

### Characteristics

Carbon monoxide, CO, is a colorless gas without taste or smell and which possesses very marked toxic properties. Compared with air, its specific gravity is 0.967. Its melting point is  $-205.7^{\circ}\text{C}$ . and it boils at  $-190^{\circ}\text{C}$ . Carbon monoxide is very slightly soluble in water (0.1178 volumes at  $40^{\circ}\text{C}$ .) and in condensability and other physical properties it closely resembles nitrogen. It is essentially a reducing substance and is employed in many metallurgical operations on this account. It has the property of combining with several metals which form carbonyls, such as iron, nickel, cobalt, molybdenum, and ruthenium. It burns in air

with a blue flame and forms an explosive mixture with air at 12.5 volumes per cent.

### Industrial Uses

Large amounts of carbon monoxide are used in industry under the designation of producer gas, which is a combustible gas containing nitrogen, carbon monoxide and small quantities of carbon dioxide, hydrogen, and methane and which is formed by passing steam or air over coal at  $1000^{\circ}\text{C}$ . Carbon monoxide is particularly important in the large scale synthesis of methanol, which is formed when a mixture of carbon monoxide and hydrogen react under high pressure, and in the presence of zinc oxide as catalyst. The most favorable proportion for this synthesis is a ratio of carbon monoxide to hydrogen of 1:2.2 and the conversion is 20 to 25 per cent. This method of synthesis of methanol has proved so successful that the production of wood alcohol by the distillation of wood has dropped almost to a negligible figure. Carbon monoxide is a constituent of city gas which in most cities in the United States contains from 6 to 30 per cent or even more of this substance. The gas from blast furnaces contains from 24 to 30 per cent carbon monoxide and the smoke from coal fire or from charcoal braziers contains variable quantities. The "after damp" resulting from explosions of coal dust contains carbon monoxide, as well as carbon dioxide. The exhaust gas of automobiles contains variable quantities of carbon monoxide depending on the adjustment of the carburetor. Diesel engine exhaust also contains carbon monoxide, although usually considerably less than that from gasoline engines.

### Toxicity

As early as 1716, the poisonous nature of gas given off by burning charcoal was recognized by Hoffmann (1) and many deaths have been caused by breathing gas resulting from imperfect combustion of a number of carbonaceous substances. Over a 10-year period (1926 to 1936), 46,925 deaths from carbon monoxide poisoning were reported in the United States (2). Exceedingly small amounts of the gas are dangerous. A concen-



tration of 0.02 per cent may produce the characteristic primary symptoms—headache and mental dullness—in a few hours' time. A concentration of 0.06 per cent may produce headache in less than an hour and unconsciousness in 2 hours while 0.10 per cent carbon monoxide may produce unconsciousness in little more than an hour and prove fatal in 4 hours. The toxic effects of carbon monoxide, which are similar to those of anoxemia, are largely due to decreased oxygen content of the blood because it combines with hemoglobin to form the very stable carbon monoxide-hemoglobin, which prevents oxygen supply to those tissues where oxygen is essential for normal body functions. Except for this, carbon monoxide is essentially a physiologically inert gas and is not a protoplasmic poison. The anoxemia resulting from the formation of carbon monoxide-hemoglobin does not cease as soon as fresh air is inhaled as with simple asphyxiants but slowly diminishes as carbon monoxide is eliminated from the blood. Carbon monoxide is not burned to carbon dioxide in the body and is only gradually eliminated from the lungs as fresh air is inhaled. The question of polycythemia following repeated exposure to low concentrations of carbon monoxide is still being actively investigated. Apparently polycythemia in man does not invariably result from repeated exposures of this type. The concentration of carbon monoxide should never exceed 100 parts per million for an 8-hour exposure, or 400 parts per million for a 1-hour exposure, in an atmosphere containing at least 19 per cent of oxygen (3).

### Analysis

The widespread nature of exposure to carbon monoxide in industry and the dangerous nature of this substance in general has stimulated investigation of convenient methods for its detection and quantitative estimation. Numerous methods have been proposed for this purpose, of which the most recent and most convenient is that developed by Martin Shepherd at the National Bureau of Standards (4). In this method, known volumes of air are drawn through small tubes containing highly purified silica gel

which, together with a palladium salt and ammonium molybdate, react to yield a series of clear-green to bluish-green colors which are easily differentiated so that an analysis may be based on an actual colorimetric procedure rather than measurements of length of tube colored. This method is capable of detecting and determining less than 1 part of carbon monoxide in 500,000,000 parts of air in 20 minutes and of detecting as little as 0.001 per cent by volume in less than 1 minute. Among other uses, this method may be employed for the rapid determination of the degree of saturation of the blood with respect to carbon monoxide. This may be done without taking a blood sample from the patient who has only to exhale alveolar air into a 20-milliliter syringe, whence it is drawn into an indicating tube for analysis. The method is also particularly useful for field determinations of carbon monoxide.

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## CARBON TETRACHLORIDE

### Characteristics

Carbon tetrachloride,  $\text{CCl}_4$ , is a colorless, clear, noninflammable, heavy, liquid with a distinctive odor. It boils at  $76.8^\circ \text{C}$ . and freezes at  $-23.0^\circ \text{C}$ . Its density is  $d_{20/4}$  1.595 and index of refraction is  $n_{20/D}$  1.4607. The vapor pressure of carbon tetrachloride reaches a value of 143 millimeters of mercury at  $30^\circ \text{C}$ . and thereafter increases nearly 100 millimeters for each 10-degrees rise in temperature until the boiling point is reached. It is slightly soluble in water, 1

cubic centimeter dissolving in 2 liters, and is freely soluble in various organic solvents. On warming with aniline and alcoholic potassium hydroxide, carbon tetrachloride yields phenyl isocyanide which has a penetrating and characteristic odor. Under the same condition, chloroform also gives off phenyl isocyanide, but much more rapidly. Carbon tetrachloride is prepared by the chlorination of methane, by the direct chlorination of carbon disulfide, or by the indirect chlorination of carbon disulfide with sulfur chloride, or as a by-product in the chlorinolysis of hydrocarbons.

### Industrial Uses

While prior to World War II the largest use of carbon tetrachloride was in dry cleaning, which accounted for approximately 45 million pounds annually, its use for this purpose has greatly decreased. Commercial dry cleaning now accounts for approximately 8 per cent of the annual output. At the present time, 56.5 per cent of the yearly consumption of carbon tetrachloride is used in the manufacture of dichlorodifluoromethane (Freon 12). The latter is largely used as a refrigerant and more lately as an insecticide dispersant (DDT). Of the total consumption of carbon tetrachloride, 11.6 per cent is used in fire extinguishers where, owing to its noncorrosive character, it is especially useful for combating fires in electrical works, or on electrical equipment. Grain fumigation accounts for 3½ per cent of the total amount used (1). Carbon tetrachloride finds extensive but decreasing use for degreasing oily machine parts and electrical equipment. It is also used in the extraction of oils from press cakes and oil seeds and for degreasing hides, bones, and garbage. Production in the United States was 234,895,000 pounds in 1954.

### Toxicity

Carbon tetrachloride is potentially toxic and prolonged, excessive, or repeated exposures to the product in any form are hazardous. It is in general a strong metabolic poison like chloroform but, while less strongly narcotic than the latter, it is much more toxic. In discussing a fatal case of carbon

tetrachloride poisoning following the accidental ingestion of this substance, Cairns (2) states that from 2 to 4 milliliters of carbon tetrachloride may constitute a fatal dose. It is easily absorbed by the mucous membrane, the lungs and, to some extent, by the skin. On inhalation in humans, it produces stupor, paresthesia of the extremities, increased secretion of saliva, weakness, fainting, and unconsciousness. Fatal poisoning may result from a single exposure to a high concentration of the vapor (3). In fatal poisoning from high concentrations, the post-mortem results show cerebral hemorrhage and edema, pulmonary edema and pulmonary emphysema, and occasionally grossly enlarged liver. Subacute poisoning may end fatally in 1 to 2 weeks. Hamburger and his associates (4) have reported serious poisoning with one fatality from the use of hair dressings containing carbon tetrachloride. In chronic poisoning which is of more immediate concern in industry, there are noticeable local symptoms of irritation of all the mucous membranes, conjunctival catarrh, nausea, vomiting, stupor, fatigue, bronchitis, and difficulty in breathing. Symptoms especially important for early diagnosis are jaundice (not invariably present in serious cases), blood changes, decreased blood calcium, increased urinary nitrogen, a limiting of the field of vision, increasing acidity of the gastric juice, and headaches. Habituation is stated to occur in workmen exposed to concentrations of from 100 to 160 parts per million (5). However, Adams *et al.* (6) recommend a limiting concentration for daily exposure of 25 parts per million. The thymol-barbital test has recently been applied in an experimental investigation of animals for the establishment of demonstrable evidence of organic damage from the inhalation of carbon tetrachloride vapor (7). McGill (8) has recently discussed six cases of carbon tetrachloride poisoning which occurred owing to inadequate safety precautions in use.

### Analysis

Most of the methods for the estimation of carbon tetrachloride depend upon its decomposition by heat in the presence of mois-



ture (9, 10) to yield hydrochloric acid, which in turn may be absorbed and titrated or estimated nephelometrically. The recent method of Cralley, Shea, and Cralley (11) permits collection of samples in the field with more simplified equipment and with no risk in atmospheres where explosive substances exist. Measured amounts of air are passed through an absorption train containing silica gel and magnesium perchlorate. The carbon tetrachloride is leached out with alcohol and decomposed with alcoholic potassium hydroxide, or a known amount of the alcoholic solution is burned, the decomposition products absorbed, and the chloride content determined by the Volhard method (Pernell, 12). A modification of the Fujiwara reaction has been described by Rogers and Kay (13) for the colorimetric determination of small concentrations of carbon tetrachloride. Fabre and his associates (14) have developed a spectrophotometric method applicable both to air sampling and to the analysis of biological material, which is based on adsorption on silica gel, followed by elutriation of the carbon tetrachloride with acetone and its reaction with alkaline pyridine.

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## CARBONYL CHLORIDE (PHOSGENE)

## Characteristics

Carbonyl chloride, phosgene,  $\text{COCl}_2$ , is a colorless, volatile liquid at temperatures below its boiling point of  $8.2^\circ \text{C}$ . It melts at  $-75^\circ \text{C}$ . and the specific gravity of the liquid is 1.392. The gas is much heavier than air, its relative density to that of air being 3.4. The gas, which is highly toxic, has a very characteristic odor resembling that of green corn. Carbonyl chloride is slightly soluble in water, in which, however, it slowly hydrolyzes. It dissolves freely in benzene, toluene, glacial acetic acid, and most liquid hydrocarbons. It is a fairly stable compound at ordinary temperatures and in the absence of moisture. Phosgene in the liquid form attacks rubber and liquid phosgene is also capable of dissolving large quantities of other toxic substances used as war gases, such as chloropicrin, diphenyl chlorarsine, and dichlorodiethylsulfide (1). Phosgene is

prepared by passing a mixture of carbon monoxide and chlorine over activated charcoal as a catalyst. The gas is easily liquified and is shipped in steel cylinders.

### Industrial Uses

The outstanding use for phosgene previously was that of a combat agent, for which purpose it was introduced by the Germans in 1915. It enters into many Friedel-Crafts syntheses with aromatics to produce acid chlorides or aryl ketones. It may also act as an agent for direct chlorination. As it reacts with organic acids, it has been used to make acid chlorides and anhydrides. With alcohols, it forms either chloroformates or carbonates.

### Toxicity

Phosgene is much like chlorine in its physiological effect, but owing to the fact that it may be inhaled more deeply with no warning symptom for the first hour or so, it is much more insidious in its action. Furthermore, it is many times more toxic than chlorine itself. More than 80 per cent of the gas fatalities of World War I were caused by phosgene (2). The physiological and toxic effects of phosgene are caused by the local hydrolysis of the material at the cell site. The hydrolytic products are hydrochloric acid and carbon dioxide. The upper respiratory passages are but slightly affected. With prolonged inhalation, however, sufficient carbonyl chloride is decomposed to produce marked inflammation and corrosion, particularly in the alveoli where the air maintains a maximum water content. Pulmonary edema appears very early. The injurious effects of carbonyl chloride are materially increased by physical exertion. Box and Cullumbine have investigated the relation between survival time and dosage with phosgene using rats and mice as experimental animals (3). They found that repeated exposures of rats and mice to sublethal concentrations of phosgene do not produce an accumulative effect (4). Weston and Karel (5) have recently evolved a biological method of assay of inhaled substances using the physiological response to phosgene as a means of measurement. Boyd

and Stewart (6) found that administration to or bathing of frogs in sodium chloride solution prevented death from phosgene and state that death from acute pulmonary edema following exposure to phosgene is probably entirely due to mechanical blockage of the respiratory surfaces by edema fluid. The experiments of Potts, *et al.* (7) appear to indicate that the lethal action of phosgene is due to acylation of essential lung constituents rather than to liberation of hydrochloric acid.

### Analysis

Phosgene may be detected as an atmospheric contaminant with the usual copper flame detector. During World War I, strips of paper which had been soaked in an alcoholic solution of *p*-dimethylaminobenzaldehyde and diphenylamine were used to detect phosgene in the air. In the presence of phosgene, the paper turns yellow to orange and will detect 1 part of phosgene per million of air. Phosgene is said to be detectable in the field by its so-called tobacco reaction (2). Smokers notice a peculiar flat metallic taste while smoking when phosgene is present in the atmosphere even in very low concentrations. Feigl (8) refers to the detection of phosgene by its conversion to diphenyl carbohydrazine which in turn gives a violet color with copper salts. This test is said to be especially useful for the determination of carbonyl chloride in commercial chloroform and carbon tetrachloride.

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## CHLORDANE

### Characteristics

Chlordane, chlordan,  $C_{10}H_6Cl_8$ , is a highly chlorinated cyclic hydrocarbon produced by reacting sodium hypochlorite with cyclopentadiene to form hexachlorocyclopentadiene, which in turn is reacted with cyclopentadiene forming hexachlorodicyclopentadiene. This is then chlorinated to about 68 per cent of chlorine and has the empirical formula  $C_{10}H_6Cl_8$ . When purified it is a pale yellow liquid with a low vapor pressure. However the commercial product is a dark brown viscous liquid with a boiling point of  $175^\circ C$ . at 2 millimeters and a density of  $D_{25}$  1.61. Its index of refraction is approximately  $n_{25/D}$  1.56. It is completely soluble in most aliphatic and aromatic solvents but is insoluble in water. It decomposes in the presence of alkali, especially when catalysed by traces of iron. The commercial product contains  $\alpha$ - $C_{10}H_6Cl_8$  (melting point  $106.5$  to  $108^\circ C$ .),  $\beta$ - $C_{10}H_6Cl_8$  (melting point  $104.5$  to  $106^\circ C$ .) and a large number of other chlorinated compounds, some of which are insecticidally inert.

### Uses

Chlordane is an insecticide used as a stomach poison, a contact poison, or as a fumigant.

### Toxicity

Stohlman, Thorp, and Smith (1) stated that the acute toxicity of chlordane is somewhat less than that of DDT when fed to rats. The approximate  $LD_{50}$  was 250 milligrams per kilogram. These investigators found degenerative changes in the intestinal submucosa and convoluted tubules of the kidneys as well as focal necrosis of the liver and congestion and edema of the lungs in

chronic poisoning. Later investigators have indicated a somewhat greater  $LD_{50}$  value for chlordane.

Chlordane acts primarily on the central nervous system with symptoms of hyperexcitability, tremors, lack of muscular coordination, and finally convulsions (2). The significant chronic toxic effects of chlordane with rats reported by Ingle (3) consist of retardation of growth rate, enlargement of the liver and kidneys, liver injury, myocardial damage and splenic alterations. Several cases of human poisoning from contact by inhalation (4), or ingestion (5, 6) have been described. One of the two fatal cases which were reported by Derbes and his associates (7) significantly indicates the rapidity of skin absorption of chlordane. In an accident in which a suspension of chlordane was spilled on her dress, a woman became confused, started having convulsions, and died within a few minutes following the accident. In a report on the present status of chlordane the American Medical Association (8) lists 15 cases of chlordane poisoning, of which four were fatal.

In contrast with the serious cases of poisoning Princi and Spurbeck (9) found that workers maintained good health in a factory manufacturing chlordane, aldrin, and dieldrin where the atmospheric concentration of the chlorinated hydrocarbons amounted to more than 5 milligrams per cubic meter. Similar findings were experienced by Alvarez and Hyman (10) in a plant where 24 men were exposed to chlordane over periods of from 2 months to 5 years with no evidence of occupational disease attributable to this substance. Ingle states that chlordane is not as toxic to warm-blooded animals as formerly because the content of the very toxic unreacted intermediate, hexachloropentadiene, is now present in less than 1 per cent in technical chlordane (11).

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## CHLORINATED DIPHENYL AND THE CHLORONAPHTHALENES

### Characteristics

Chlorinated diphenyl is prepared by the direct replacement of one or more of the hydrogen atoms of diphenyl,  $C_6H_5 \cdot C_6H_5$ , by chlorine. Chlorination may proceed until all the hydrogen atoms have been replaced. The greater the amount of chlorine introduced, the higher the melting point, and the more the substance becomes resinous or waxy in nature. The chlorinated naphthalenes vary in physical state from a thinly fluid, mobile liquid to a crystalline or amorphous wax, and vary in properties according to the degree of chlorination. The above chlorinated waxes are free from moisture, do not absorb water, are neutral and noncorrosive to metals, do not support combustion, are high in dielectric strength, and have an extraordinary specific inductive capacity. They are marketed under such trade names as "Arochlor", "Halowax", and "Seekay". The melting points of the chlorinated naphthalenes vary from  $87^\circ$  to  $130^\circ$ , and the boiling points from  $288^\circ$  to  $371^\circ$  C. The specific gravity ranges from 1.4 to 1.7. They are soluble in many organic solvents and oils, especially when heated together.

### Industrial Uses

These substances have wide application in industry, chiefly owing to their special insulating and water-resistant properties, their chemical stability, and their flame resistance. They are especially used in condensers and in the insulation of wires and cables used in war ships. To a certain extent they are used as solvents for rubber or aniline, as well as for varnish, gums, and resins when mixed in the molten state.

### Toxicity

Poisoning by the chlorinated naphthalenes may take the form of acne, particularly of the face, or of toxic jaundice produced by necrosis of the liver. As early as 1918, an acne-form eruption of the skin noted among workers handling chloronaphthalene was ascribed to this substance. Jones has pointed out that in the absence of cleanliness, chloronaphthalene irritated the sebaceous glands causing an excess of cell growth and secretion followed by plugging of the gland and possible secondary infection (1). Schwartz in 1936, discussed dermatitis of workers in the chloronaphthalene and chlorodiphenyl industry. He reported a further outbreak of "Halowax acne" or "cable rash" among electricians installing heat and flameproof cables on ships in 1943 (2, 3).

Systemic poisoning from these chlorinated substances usually follows the inhalation of fume rather than from the handling of the dry hydrocarbon waxes. Damage is severe and occasionally fatal. Acute yellow atrophy of the liver is generally associated with serious exposure to the chlorinated naphthalenes and diphenyl fumes. Three fatalities were reported in 1936-1937 (4, 5). In 1939, three additional cases were reported by Greenburg, Mayers, and Smith (6) and a further case by Collier in 1943 (7). While acne may be taken as a warning sign in workers handling this material it is not invariably present and systemic poisoning may occur in the absence of this sign. Hunter recommends the medical supervision of all such workers with special care regarding the hygienic conditions of employment and with adequate



ventilation (8). Precautionary measures were suggested for workers handling chlorinated naphthalenes and diphenyl compounds in 1943 by Greenburg (9). Nomura (10) found that the toxicity of chlorinated naphthalene increased with a higher degree of chlorination, with which however there is a decrease in solubility and volatility. Meigs, *et al.* (11) noted seven cases of mild to moderate chloracne among 14 chemical workers exposed intermittently to small concentrations of the vapor of Arochlor (chlorinated diphenyl). This substance absorbed through the skin of rabbits causes fatty degeneration of the liver (Paribok, 12).

### Analysis

The fume content of the air following the heating of chlorinated diphenyl or chlorinated naphthalenes may be determined by the catalytic decomposition of this material followed by suitable determination of the inorganic chloride formed. In such cases, however, the chlorine content and hence the composition of the chloro derivative in use must be known since one or more of a whole series of chloro compounds of varying chlorine content may be present. In the presence of more than one chloro derivative, this method can only be taken as a rough index of the amount of contaminant present.

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## THE CHLORINATED MONO-NITROPARAFFINS

### Characteristics

The four chloronitroparaaffins which are of some industrial importance are listed together with their physical properties in Table 4.

### Industrial Uses

The four chloronitroparaaffins listed above are more active as solvents than the straight nitroparaaffins. 1-Chloro-1-nitropropane will dissolve many synthetic rubbers, including Buna N, Chemigum, Hycar O. R., and some grades of Neoprene. The chloronitroparaaffins are also used in the synthesis of other chemicals, such as chloronitroalcohols. 1,1-Dichloro-1-nitroethane, under the trade name of Ethide, is a fumigant said to have good penetration properties and is used in the fumigation of stored grains, flour, and tobacco. A distinct warning odor and high flash point, in addition to its insecticidal properties, make it especially valuable for this purpose. The addition of 1-chloro-1-nitropropane to rubber cements confers useful anti-gelling properties (1).

### Toxicity

The symptoms produced in animals by the administration of 1-chloro-1-nitroethane and 2-chloro-2-nitropropane by stomach tube were found by Machle and his associ-

TABLE 4

	1-Chloro-1-nitroethane	1-Chloro-1-nitropropane	2-Chloro-2-nitropropane	1,1-Dichloro-1-nitroethane
	NO <sub>2</sub>   CH <sub>3</sub> CHCl	NO <sub>2</sub>   CH <sub>3</sub> CH <sub>2</sub> CHCl	NO <sub>2</sub>   CH <sub>3</sub> CClCH <sub>3</sub>	NO <sub>2</sub>   CH <sub>3</sub> CCl <sub>2</sub>
Formula.....	CH <sub>3</sub> CHCl	CH <sub>3</sub> CH <sub>2</sub> CHCl	CH <sub>3</sub> CClCH <sub>3</sub>	CH <sub>3</sub> CCl <sub>2</sub>
Molecular weight.....	109.52	123.54	123.54	143.97
Density $\rho_{20/20}$ .....	1.258	1.209	1.193	1.405
Boiling point °C.....	127.5	139.5	133.6	124
Refractive index 20°C.....	1.423	1.430	1.425	1.441
Flash point °C.....	56.1	62.2	57.2	75.6
Solubility water 20°C. (ml./100 ml.).....	<0.4	<0.8	<0.5	<0.5
Vapor pressure 25°C. (mm. of Hg) (2).....	11.9	5.8	8.5	16

ates (2, 3) to be similar to those produced by the simple nitroparaffins, *i.e.*, progressive weakness and collapse, unsteadiness, incoordination, and changes in respiration—with the exception that incoordination was slightly less evident than with the nitroparaffins. Weakness and depression were the outstanding signs. The lethal dose for rabbits of 1-chloro-1-nitroethane administered orally lies between 0.10 and 0.15 gram per kilogram and that for 2-chloro-2-nitropropane is between 0.50 and 0.75 gram per kilogram. Skin application did not result in any systemic effect, weight loss, or skin irritation. In a further investigation of the chlorinated mononitroparaffins, Machle and his associates (2) found the lethal oral dose of 1,1-dichloro-1-nitroethane for rabbits to be between 0.15 and 0.20 gram per kilogram. The lethal oral dose of 1-chloro-1-nitropropane for rabbits was found to be between 0.05 and 0.10 gram per kilogram. 1,1-Dichloro-1-nitroethane was found to be a skin irritant but 1-chloro-1-nitropropane has no such effect. Both compounds are lung irritants, however, and in high concentrations they rapidly produce pulmonary edema. Exposure to the vapor of 1,1-dichloro-1-nitroethane in concentrations in excess of 0.3 milligram per liter for longer than 1 hour is dangerous to rabbits. However, the vapor of 1-chloro-1-nitropropane was found to be considerably less toxic. Apart from the injury of the lungs produced by the inhalation of these substances, the liver, heart, kidneys,

and vascular system are all involved in acute toxic damage.

### Analysis

1-Chloro-1-nitropropane reacts with phenylhydrazine in concentrated sulfuric acid to produce a deeply colored red substance, which may be measured photometrically (2). The color developed by the oxidation of resorcinol by 1,1-dichloro-1-nitroethane in methyl alcohol may similarly be made the basis for the determination of this substance (2).

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## CHLOROACETONE

### Characteristics

Chloroacetone, monochloroacetone, 1-chloro-2-propanone, acetyl chloride, CH<sub>3</sub>—CO—CH<sub>2</sub>Cl, is a colorless liquid boiling at 119° C. and having a density of  $\rho_{25/4}$  1.123 and a melting point of -44.5° C. It has a penetrating, very pungent odor resembling hydrochloric acid. Monochloroacetone



is only slightly soluble in water and tends to polymerize to a dark and relatively inert resinous form in contact with it. It is soluble in alcohol, in ether, and in chloroform. It is prepared by conducting chlorine gas into cold acetone in the presence of calcium carbonate, or by the action of calcium hypochlorite on acetone. It is also prepared by the electrolysis of acetone and hydrochloric acid.

### Toxicity

Monochloroacetone is a lachrimatory substance and was introduced by the French as a war gas in World War I but was soon replaced by monobromoacetone and other more powerful lachrimators. As a war gas it had the advantage that it is nearly four times as heavy as air and that it causes severe conjunctivitis in concentrations as low as 5 parts per million of air. A concentration of 26 parts per million is intolerable after 1 minute of exposure and a concentration of 607 parts per million is lethal after 10 minutes of exposure. The main irritation from this substance is limited to the upper respiratory tract. Monochloroacetone will blister the skin on contact and adequate precautions should therefore be taken in handling this substance. While the use of this compound is limited in industry, and even though its powerful lachrimatory character serves as a warning agent, its possible lethal action should be considered in those cases where it is to be stored or handled in quantity.

## CHLOROBENZENE

### Characteristics

Chlorobenzene, benzene monochloride, monochlorobenzene,  $C_6H_5Cl$ , is a clear, colorless, mobile, somewhat volatile liquid with a not unpleasant almond-like odor. It boils at 131 to 132° C., melts at -45° C., has a specific gravity of  $d_{20/4}$  1.107, and index of refraction of  $n_{20/D}$  1.5248, and a flash point of 28° C. It is insoluble in water but dissolves freely in alcohol, chloroform, benzene, and ether. Monochlorobenzene is produced by the direct chlorination of benzene

to which a small aluminum-mercury couple is added as a carrier, with subsequent neutralization of the hydrochloric acid by means of caustic soda. Molybdenum chloride is also used as a catalytic agent for the chlorination of benzene.

### Industrial Uses

Relatively large amounts of monochlorobenzene are produced industrially. In 1953, production in the United States amounted to 377,184,000 pounds. Monochlorobenzene is used in solvent mixtures and as a method of producing crackle or matt effects in lacquers, as a solvent for ethyl cellulose and resins, oils and fats, and for the commercial synthesis of phenol, aniline, picric acid, and other intermediates used in the production of dyestuffs, drugs, and perfumes. It is a basic material in the manufacture of DDT.

### Toxicity

While Flury and Zernik (1) concluded from the early experimental work by Götzmann on cats, together with certain later reports, that monochlorobenzene was somewhat more toxic than benzene itself, Hunter (2) states that monochlorobenzene is less toxic than benzene and has caused no trouble in industry. Acute symptoms due to accidental swallowing of a small amount of monochlorobenzene by a child were described by Reich in 1934 (3). The symptoms disclosed in this case indicate that monochlorobenzene is a central nervous poison. Unconsciousness lasting for 3 hours, cyanosis, loss of reflexes, and twitching of the facial muscles were followed by gradual recovery. Cases where the inhalation of chlorobenzene vapors produced injury appear to be complicated by the fact that other chloro derivatives, such as *o*- and *p*-dichlorobenzol, were present. Chlorobenzene is excreted unchanged through the lungs of rabbits to the extent of 25 to 30 per cent following the administration of doses amounting to 0.5 gram per kilogram of body weight, according to Azouz and his associates (5).

### Analysis

Monochlorobenzene may be detected when present in sufficient amount by one of

its identifying derivatives. On warming to 80 to 90° C. with nitric acid in concentrated sulfuric acid, it yields the 2,4-dinitro-derivative having a melting point of 52° C. On adding to a large excess of chlorosulfonic acid in the cold, monochlorobenzene yields the *p*-sulfochloride (melting point 53° C.) which with ammonium hydroxide yields the sulfonamide (melting point 143° C.). Monochlorobenzene may be detected as an aerial contaminant in the absence of other halogenated compounds by means of a flame detector. Smyth (4) has checked the thermal decomposition method for the determination of the vapor of monochlorobenzene in air and found that this method is satisfactory over a range of from 12 to 18,500 parts per million. A spectrophotometric method for determining chlorobenzene in expired air has recently been described (5).

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## 2-CHLORO-1,3-BUTADIENE

### Characteristics

2-Chloro-1,3-butadiene, chloroprene,  $\text{CH}_2=\text{CH}-\text{CCl}=\text{CH}_2$ , is a clear, colorless liquid possessing an odor somewhat similar to ethyl chloride and having the following properties: density  $d_{20/4}$  of 0.9583, refractive index  $n_{20/D}$  of 1.4583, and boiling point of 59.4° C. It may be synthesized from acetylene which is commercially prepared by passing vinyl acetylene in gaseous form through a solution of cuprous chloride with ammonium chloride in concentrated hydrochloric acid at a temperature of 30° C. The chlorobutadiene is distilled and purified by redistillation following the addition of a small amount of pyrogallol. Liquid chloroprene polymerizes spontaneously with

no other catalyst than a small amount of air to a tough and dense jelly-like substance. An artificial latex may be produced from chloroprene emulsified in water with a small percentage of sodium oleate. The droplets soon polymerize yielding a colloiddally dispersed neoprene, which may be stabilized by adding sulfonated abietene.

### Industrial Uses

Although its chief commercial importance lies in its ability to polymerize to a rubber-like substance variously called Neoprene or Duprene, chloroprene yields several other different types of polymers. The vulcanizates of this synthetic rubber are very resistant to heat, oils, sunlight, and ozone, and therefore not only serve as a substitute for natural rubber but have superior properties for certain purposes. This durability under conditions which cause natural rubber to deteriorate rapidly makes neoprene especially suitable for use in diaphragms, gaskets, and washers where these materials may come into contact with oil.

### Toxicity

According to Henderson and Haggard (1), the vapor of chloroprene is irritating but this does not entirely obscure its anesthetic action. The mechanism of its action has been studied by von Oettingen and his associates (2), who found that chloroprene causes depression of the central nervous system and severe irreparable damage of most vital organs which, even with small doses, may be severe enough to cause death. Inhalation of the vapor causes primary irritation of the respiratory tract, followed by progressive depression of the respiration and asphyxia. A concentration of 1 milligram per liter is considered dangerous and continued exposure to a concentration of 0.3 milligram per liter or even less may cause toxic effects. These investigators found that chloroprene may be absorbed through the skin to such an extent that acute and chronic effects may follow such exposure. The early detection of incipient poisoning is based on determination of the icteric index of the blood at intervals and testing of the urine for albumen, reducing substances, and bile



pigments, as well as frequent determination of the blood pressure. Low blood pressure may indicate possible incipient poisoning. Investigation of the toxicity of crude Duprene has shown that this polymerization product is practically void of toxic properties and that contact with Duprene rubber sheeting is not likely to cause irritation of the skin (3). Schwartz (4), investigating the skin hazards in the manufacture of synthetic rubber, found comparatively little dermatitis in 20 plants inspected. Neoprene latex, however, as used in patch tests produced some positive skin reactions. Loss of hair has been noticed among employees engaged in making one of the synthetic rubbers. Ritter and Carter (5) determined that hair loss is not caused from industrial exposure to either the monomeric form of chlorobutadiene or its commercial polymer, neoprene, but results exclusively from work in areas where chlorobutadiene is being polymerized. This hair loss may be controlled or even eliminated by frequent and complete changes of air in the polymerization areas.

### Analysis

Determination of the concentration of chloroprene as an atmospheric contaminant may be made by any one of the various methods used for halogenated hydrocarbons. Alekseeva and Andronov (6), as well as Senderikhina (7), have discussed in detail specific methods for the determination of chloroprene vapor in air. Hanson (8) has applied the ultraviolet photometer to the quantitative measurement of small traces of chloroprene in air. The sensitivity of this photometric method was found to be 0.5 part per million for 1 scale division of the instrument.

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## CHLOROFORM

### Characteristics

Chloroform, trichloromethane,  $\text{CHCl}_3$ , melting point  $-63.5^\circ \text{C}$ ., boiling point  $61.3^\circ \text{C}$ ., density  $d_{15/4}$  1.49845, index of refraction  $n_{20/D}$  1.4476, is a colorless, clear, highly refractive, heavy, very volatile, sweet-tasting liquid with a characteristic odor. The liquid is not inflammable but the vapor is capable of burning. The vapor pressure at  $20^\circ \text{C}$ . is 160 millimeters of mercury. Its solubility in water is approximately 5 milliliters per liter at  $25^\circ \text{C}$ . It is miscible with alcohol, benzene, ether, petroleum ether, carbon tetrachloride, carbon disulfide, and oils. On exposure to air and sunlight, chloroform is slowly oxidized to the highly toxic substance, phosgene. Commercial preparations are stored in brown bottles and contain 0.6 to 1 per cent of alcohol to destroy traces of phosgene formed in storage. Chloroform is made industrially by the haloform reaction, which consists in the treatment of acetone or ethanol with either bleaching powder or a solution of sodium hypochlorite, or by the reduction of carbon tetrachloride with iron in the presence of moisture. The latter is the more important process and is now the principal source of chloroform. On warming with aniline and potassium hydroxide, chloroform yields phenylisocyanide which has a foul and characteristic odor. When chloroform is warmed with resorcinol in dilute sodium hydroxide, a red color is obtained. It also gives a deep red color when warmed with a sodium hydroxide solution and pyridine.

### Industrial Uses

Chloroform is a general inhalation anesthetic which was formerly widely used. Medicinally, it is also employed as an anodyne, antispasmodic, and analgesic. Commercially, it serves as a solvent for fats, oils, iodine, alkaloids, waxes, gutta-percha, and resins, but its uses as a solvent are only of minor importance. However, it is used as a lacquer solvent, in the artificial silk and plastics industries, as a constituent of floor polishes, and, to some extent, as a cleaning fluid. During 1954, production of chloroform in the United States amounted to 32,087,000 pounds.

### Toxicity

The introduction of chlorine atoms in place of the hydrogen in methane produces substances with marked narcotic properties. Chloroform itself is a powerful anesthetic but has secondary toxic effects which are exercised primarily on the liver. The prolonged administration of chloroform as an anesthetic may lead to such serious effects as profound toxemia and damage to the liver, heart, and kidneys. Davis and Whipple (1) found that prolonged but light chloroform anesthesia in dogs produced a typical hepatitis. Inhalation of concentrated chloroform vapor results in irritation of the mucous surfaces exposed to it. Ordinary narcosis is usually preceded by a stage of excitation, which is followed by loss of reflexes, sensation, and by unconsciousness. The after effects consist of gastrointestinal disturbances, pain in the liver region, jaundice, and, following severe and continued exposure, acute yellow atrophy of the liver. A form of chronic chloroform addiction exists due to the misuse of chloroform but no chronic effects of this type have been found to exist in industry. Miller and Whipple (2) found that dogs which had been depleted of plasma proteins were abnormally susceptible to chloroform poisoning and that the administration of methionine protected them even when given up to 4 hours after chloroform administration. Some liver damage followed the administration of the chloroform, but instead of the condition progressing to a fatal issue the icteric index began to fall

after 72 hours and the animals recovered. The authors suggest that protein depletion removes more sulfur than nitrogen from the liver and that this deficiency of sulfur is the cause of the chloroform susceptibility. There is no evidence that methionine will protect a normal liver against chloroform (3). Experiments on rats given sublethal doses of chloroform have indicated that 2,3-dimercaptopropanol (BAL) administered orally has no protective or antitoxic action against chloroform vapor (4). It is of interest that chloroform has been found as a metabolism product of inhaled trichloroethylene by Soucek and Vlachova (5). A new method for the determination of chloroform in the presence trichloroethylene, based on Fujiwara's reaction, has been proposed by these authors. According to Henderson and Haggard (6), 4,000 parts per million causes slight symptoms after 8 hours of exposure and these investigators recommend allowable concentration of from 40 to 100 parts per million.

### Analysis

Chloroform may be detected after suitable trapping from air samples by application of one of the reactions described under "characteristics" above. Gravimetric and volumetric methods depend on the hydrolysis of the chloroform and quantitative precipitation of the resulting chloride ion by addition of a suitable soluble silver salt. Chloroform reacts with  $\alpha$  or  $\beta$  naphthol in alkaline solution to give an intense blue color. Although the  $\alpha$  compound is more sensitive, the  $\beta$  compound gives better colors and is less subject to interference. The presence of 1 to 3 milligrams of chloroform may be detected by this procedure. Habgood and Powell (7) have devised a method for the measurement of chloroform, carbon tetrachloride, and trichloroethylene in blood. Quantities of these substances varying between 2 and 0.02 milligram can be recovered from the blood with an accuracy within  $\pm 5$  per cent.

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## THE CHLORONITROBENZENES

### Characteristics

The chloronitrobenzenes,  $\text{ClC}_6\text{H}_4\text{NO}_2$ , exist in three isomeric forms. These substances are crystalline in form and yellow in appearance. The properties of the various chloronitrobenzenes which are of commercial importance are summarized in Table 5.

The chloronitrobenzenes are prepared either by chlorinating nitrobenzene in the presence of iodine or by nitrating chlorobenzene. 1-Chloro-2,4-dinitrobenzene,  $\text{C}_6\text{H}_3\text{Cl}(\text{NO}_2)_2$ , is prepared by nitrating chlorobenzene first to *o*- and *p*-chloronitrobenzenes, both of which yield the 2,4-dinitro compound upon further nitration.

### Industrial Uses

The chloronitrobenzenes are used for organic syntheses and are chiefly of interest in the explosives industry. A liquid mixture of a large amount of the *o* compound with a smaller amount of the *p* derivative is designated as Tropfoel in this industry. In chlorodinitrobenze, the chlorine is active and

this substance readily yields dinitrophenol by hydrolysis and dinitroaniline by reaction with ammonia. This substance may be nitrated to an explosive by replacement of the chlorine group and therefore has a definite advantage over picryl chloride (1). It is extensively used in the dyestuff industry. The production of 1-chloro-2,4-dinitrobenzene rose to a maximum of 37,215,000 pounds in 1943 and declined to 14,123,000 pounds in 1945 in the United States.

### Toxicity

Exposure to the chloronitrobenzenes in industry is chiefly related to the dust of these substances (2). The chloronitrobenzenes have an aromatic odor and a toxic action similar to that of the parent substance. They are more poisonous, however, than nitrobenzene and the dust of chlorodinitrobenzenes is potentially more toxic than that of the chloronitrobenzenes. The *p*-chloronitrobenzene is somewhat less toxic than the *o* compound. The inhalation of the vapor of the *o*-chloronitro compound in concentrations of from 8 to 30 parts per million was fatal to cats following a total exposure of 17.5 hours. On the other hand, the inhalation of 31 parts per million of the *p* compound for the same length of time by cats indicated only some sleepiness and slight indisposition (3). Renshaw and Ashcroft (4) report four cases of poisoning in man following exposure to mononitrochlorobenzene vapor in a chemical plant engaged in the manufacture of *o*- and *p*-chloronitrobenzene. These investigators concluded that mononitrochlorobenzene is a blood poison and that its effect is cumulative. The toxic effects appeared in all cases after leaving work and were characterized by cyanosis and collapse. Dyspnea on exertion appeared

TABLE 5

Substance	Melting Point °C	Boiling Point °C.	Density d 20/4	Solubility	
				Water	Alcohol
<i>o</i> -Chloronitrobenzene	32.5	245	1.368	Insoluble	Soluble
<i>m</i> -Chloronitrobenzene	44.0	235	1.534	Insoluble	Soluble in hot alcohol
<i>p</i> -Chloronitrobenzene	83.5	242	1.520	Insoluble	Soluble in hot alcohol
1-Chloro-2,4-dinitrobenzene	52.54	315	1.697	Insoluble	Soluble

later and recovery occurred only after some weeks. The authors concluded that a stable compound was formed with hemoglobin giving rise to a peculiar cyanotic condition and collapse from oxygen deficiency. In six cases of industrial poisoning with chloronitrobenzene Spaun (5) reported malaise and cyanosis present in all cases with mild to severe anemia. Werner and Wetzel (6) report five cases with lowered red cell counts but no liver damage. While *p*-chloronitrobenzene caused methemoglobinemia and hemolytic anemia in cats chronically exposed to about 3 parts per million, Watrous and Schulz (7) state that it does not affect workers exposed intermittently to levels averaging 14 parts per million. The dust of 1-chloro-2,4-dinitrobenzene is a severe irritant to the mucous membranes. No maximum allowable concentration value for the chloronitrobenzenes has been established.

### Analysis

The three chloronitrobenzenes may be distinguished and identified by the formation of characteristic derivatives. On treatment with zinc dust and dilute acetic acid, the *o*, *m*, and *p* compounds yield, respectively, *o*-chloroaniline (boiling point 207° C.), *m*-chloroaniline, boiling point 230° C.), and *p*-chloroaniline (melting point 70° C.). On boiling with potassium hydroxide in methyl alcohol, they yield, respectively, *o*-nitroanisole (melting point 9 °C.; boiling point 265° C.), 3:3'-dichloroazoxybenzene melting point 97° C.), *p*-nitroanisole (melting point 54° C.), and some 4:4'-dichloroazoxybenzene (melting point 155° C.). 1-Chloro-2-,4-dinitrobenzene is a useful reagent for primary and secondary amines and for mercaptans and advantage can be taken of this for identification or determination of the dinitro derivatives.

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## CHLOROPICRIN

### Characteristics

Chloropicrin, trichloronitromethane, nitrochloroform,  $\text{CCl}_3\text{NO}_2$ , is a colorless, slightly oily liquid possessing a very intense and penetrating odor and having a pronounced lacrimatory action. It boils at 112° C., has a density  $D_{20/4}$  of 1.6517, melts at -69° C., and has a refractive index of  $n_{23/D}$  1.46075. It dissolves in water to the extent of only 0.25 per cent, but is freely soluble in alcohol and ether. On boiling with dilute potassium hydroxide, chloropicrin yields potassium nitrite and potassium chloride. On warming a drop of chloropicrin with thymol in alcoholic potash, a yellow color is obtained, while resorcinol in place of thymol yields a red color. Chloropicrin, when treated with iron and acetic acid, yields methylamine. According to Gould and his associates (1), the vapor pressure of chloropicrin at 25.5° C. is 24 millimeters of mercury, while at 55.0° C., it is 100 millimeters of mercury.

### Industrial Uses

Apart from its use as a potential war gas, chloropicrin is used for the synthetic preparation of a number of organic substances and particularly for the manufacture of the dyestuff known as methyl violet. Chloropicrin has also been used in the form of water emulsions with soap as sprays to control insects. It is slower in action than hydrocyanic acid and unfortunately is relatively toxic to living plants and seeds. Although it evaporates fairly rapidly at ordinary temperatures and its vapor pressure is relatively great (18.3 millimeters of mercury at 20° C.), it evaporates from soil somewhat slowly. In the open, its volatility at 20° C. is 165 milligrams per liter at equilibrium.



The decomposition of trichloronitromethane ( $\text{CCl}_3\text{NO}_2 + \text{O} + 2\text{H}_2\text{O} \rightarrow 3\text{HCl} + \text{CO}_2 + \text{HNO}_3$ ) is aided by certain substances, such as arable soil, milk, and cereals. In 1 kilogram of garden soil, 0.5 gram of trichloronitromethane disappears in 6 days and with the addition of 20 per cent water, it disappears in 2 days (2). The present practice consists in injecting small measured portions of chloropicrin into the soil with proper spacing at a depth of about 6 inches some time prior to the planting of seed crops. It is also used for sterilizing seed beds.

### Toxicity

Chloropicrin is a pronounced irritant to all body surfaces. In addition to skin irritation, it causes lacrimation, vomiting, bronchitis, and pulmonary edema. In a concentration of 1 part to 1 million parts of air, it causes a smarting pain in the eyes and therefore, in itself, constitutes a warning of exposure. The vomiting tendency is probably due to swallowing saliva in which small amounts of chloropicrin have dissolved. Because of this property, chloropicrin was called "vomiting gas" and was extensively used in World War I. The vomiting tendency caused soldiers to remove their gas masks and they therefore became exposed to the more noxious gases which accompanied chloropicrin. Apart from this desired property of chloropicrin as a war gas, it is, in itself, a lethal substance acting primarily to produce lung injury. Owing to its chemical inertness, chloropicrin does not react with the usual chemicals used in gas masks to protect against war gases and is removed only by charcoal. It was therefore one of the most difficult of the war gases to protect against. The after-effects of exposure by inhalation to chloropicrin may be serious. These may consist of anemia, weak and irregular heart, and recurrent asthmatic attacks. A concentration of 4 parts per million was sufficient to render a man unfit for action, according to Flury and Zernik (3) and 20 parts per million when breathed for more than 1 or 2 minutes causes definite bronchial or pulmonary lesions (4). In addition, chloropicrin reacts with all the SH-groups of the globin of reduced hemoglobin

and also with the oxygen-carrying group, rendering it incapable of carrying oxygen (5). With the more recent extensive use of chloropicrin as a soil fumigant and disinfectant, as well as for fungicidal and bactericidal purposes, attention should be directed towards its physiological and possible lethal effect on man. In this connection it is of interest that Moureu and his associates (6) found an instance of photochemical transformation of chloropicrin into phosgene in the case of a dwelling which had undergone disinfection with chloropicrin to free the house from lice. No threshold limit has been established for chloropicrin.

### Analysis

Chloropicrin reacts with dimethylaniline to give a yellow-red color. Test papers soaked in this reagent were used as detectors for this substance as a war gas. A variety of other substances, such as chlorine, bromine, and nitrous gases, also react somewhat similarly with dimethylaniline and must be absent. Quantitatively, chloropicrin may be determined by passing it into a solution of sodium sulfite, which converts it to the sodium salt of formyl trisulfonic acid and sodium chloride. The inorganic chloride may be determined by the usual Volhard titration. Danner and Goldenson (7), using a specially prepared charcoal, adsorb chloropicrin effectively by means of a sampling apparatus through which the contaminated air is drawn. The analysis of the sample is made by combustion in an electric furnace and the chlorine of the decomposed vapor is absorbed by a sodium sulfite solution and determined as above. Moureu *et al.* (8) have developed test papers to indicate both chloropicrin and phosgene, whether the gases are present singly or together. Chloropicrin test papers are impregnated with a solution of pyridine-methanolic phloroglucinol and sodium cyanide. In the presence of less than 50 milligrams per cu. meter a rose tint develops. Phosgene papers are impregnated with an alcoholic solution of *p*-dimethylaminobenzaldehyde and dimethylaniline and will detect 10 milligrams per cubic meter of phosgene in the air in 1 minute.

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## CRESOLS—CRESYLIC ACID

## Characteristics

Cresol, cresylol, tricresol, cresylic acid, hydroxytoluene,  $C_6H_4CH_3OH$ , is a mixture of the three isomers—*o*-, *m*-, and *p*-cresol. It has a specific gravity of 1.032 to 1.038 at 25° C. and distills between 190° and 205° C. It is a colorless, yellowish, brownish, or pinkish liquid, having a phenolic odor and darkening on exposure to light. Its solubility in water is about 2 per cent and it is miscible with alcohol, benzene, ether, and glycerol. It is also soluble in solutions of the alkali hydroxides. The cresols and cresylic acid are derived from coal tar for the greater part. They are also obtained to some extent from petroleum. Cresylic acid is the redistilled higher boiling portion of the crude phenolic liquor. The principal characteristics of the constituent cresols are as follows:

*o*-Cresol, *o*-cresylic acid, *o*-oxy-toluene, *o*-methyl phenol, consists of colorless crystals darkening with age and exposure to air and light. Its density  $d_{20/4}$  is 1.047. It melts at 30° C., boils at 191 to 192° C., and has a flash point of 81 to 83° C. Its index of refraction  $n_{20/D}$  is 1.553. It is soluble in about forty volumes of water. In common

with the other cresols, *o*-cresol is obtainable from coal tar. *o*-Cresol is volatile with steam and is not dissolved by 5 parts of ammonium hydroxide which differentiates it from phenol. It gives a violet-blue coloration with ferric chloride changing later to a turbid brown. With bromine water, it yields 4,6-dibromo-2-methyl phenol (melting point 56 to 57° C.). In alcohol with a strong solution of picric acid in 50 per cent alcohol, it yields orange or yellow needles of the picrate (melting point 88° C.). This differentiates *o*-cresol from *p*-cresol. The latter is unstable under these conditions and does not form a precipitate.

*m*-Cresol, *m*-cresylic acid, *m*-oxy-toluene, *m*-methyl phenol, is a colorless to yellow liquid having a boiling point of 202.7° C., a melting point of 11.95° C., density  $d_{20/4}$  of 1.03401, and an index of refraction of  $n_{15/D}$  1.54318. It is soluble in alcohol, ether, and chloroform and dissolves in about 40 volumes of water. It is not soluble in 5 parts ammonium hydroxide which differentiates it from phenol. It gives a blue-violet color with ferric salts which is fairly permanent. When treated with bromine water, *m*-cresol yields 2,4,6-tribromo-3-methyl phenol which, when crystallized from alcohol, has a melting point of 84° C.

*p*-Cresol, *p*-cresylic acid, *p*-oxy-toluene, *p*-methyl phenol, is a white crystalline mass similar to phenol in odor, obtained as in the case of the other cresols by the fractional distillation of crude cresol or by fusing *p*-toluene-sulfonic acid with potassium hydroxide. It melts at 36° C. and boils at 202.32° C. Its solubility in water at 40° C. is about 2.2 per cent. It is freely soluble in alcohol, ether, and chloroform. Its specific gravity is 1.039. It gives a blue-violet color with ferric chloride, later becoming turbid. With bromine water, it yields 2,6-dibromo-4-methyl phenol crystallizing in needles from petroleum and having a melting point of 48 to 49° C.

## Industrial Uses

The chemical allocation records of the War Production Board for the years 1943, 1944, and half of 1945 show that the amount of cresols and cresylic acid used ranged be-



tween 103 and 110 million pounds per year. Of this, 20 million pounds was imported. Sixty-two per cent of the 1944 allocation was used in chemical manufacture (phenolic resins, 34 per cent; and tricresyl phosphate, 28 per cent). Other uses included ore flotation (9.4 per cent), carbon remover (9 per cent), disinfectant (7.9 per cent), and oil refining (3.4 per cent). Smaller amounts were used in the textile, medicinal, and dye and ink industries. The total production of cresols and cresylic acid in the United States amounted to 69,930,000 pounds in 1954.

### Toxicity

The cresols are well known for their germicidal power which averages three or four times that of phenol. The introduction of the alkyl group is apparently responsible for their increased germicidal activity. The toxicity of the mixed cresols is, however, somewhat less than that of phenol, otherwise they produce identical effects and lesions. Individually considered, *m*-cresol is less poisonous and less irritant than phenol, while *o*-cresol is more toxic and *p*-cresol is the most toxic of all three. These differences are too small to be of any great practical importance. The symptoms following ingestion are similar to those of phenol collapse, exhaustion followed by coma, and death. Marked alterations have been found in the liver and nephritis and hemolysis have been noted. The principal exposure in industry is related to skin contact. Burns (1) or skin irritation (2, 3) have frequently been reported. This often is the result of handling wood painted with a crude creosote which contains cresol. This material, which is a good wood preservative, is applied under pressure. Sawing such wood produces an irritant sawdust. Roofing paper is sometimes similarly treated with crude cresol. Corcos (4) found that workers manufacturing an artificial resin containing cresol complained of headache, tremor, and vomiting. Some pathology of the kidneys with moderate hypertension was evident and phenolic material was found in the urine. Birdwood (5) has reported cases of keratitis resulting from contact with cresol-containing spray. Droplets of spray produced small gray spots

on the cornea and there was impairment of vision. When the droplets got into the eyes there was intense irritation and great pain.

### Analysis

Maevskaya (6) has devised a method for determining the cresol content of air, which consists in collecting a large sample of air in a flask containing sodium hydroxide which is then neutralized with acetic acid and treated with *p*-nitroaniline. An equivalent of sodium nitrite solution is then added, followed by sodium carbonate solution. The rose-red coloration is compared with cresol standards. Using the ultraviolet absorption spectra of vapors, a method for the quantitative analysis of isomeric cresols and cresol-phenol mixtures has been developed by Robertson and his associates in which the mean deviation between the known composition of these mixtures and the values determined from the working curves is less than 2 per cent (7).

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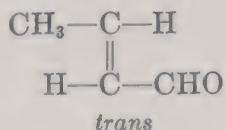
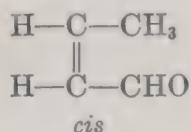
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## CROTONALDEHYDE

### Characteristics

Crotonaldehyde, 2-butenal, crotonic aldehyde, propylene aldehyde, or  $\beta$ -methylacrolein is a colorless, flammable liquid with a sharp, characteristic pungent and irritating odor, freezing at  $-69^{\circ}\text{C}$ . and boiling at  $102.2^{\circ}\text{C}$ . Its density is  $d_{20/20}$  0.853, index of refraction  $n_{17.3/D}$  1.4384, and it has a vapor pressure of 30 millimeters of mercury at  $20^{\circ}\text{C}$ . Crotonaldehyde can exist

either in the (*cis*) form or the (*trans*) form



but the substance found in commerce has the *trans* configuration. The flash point (open cup) of anhydrous crotonaldehyde is 13° C. Its solubility in water is 18.1 grams per kilogram at 20° C. Crotonaldehyde slowly oxidizes to crotonic acid in the open air and this oxidative process increases in rate with increased pressure, or in the presence of catalysts. As might be inferred from its ethylenic structure and aldehyde group, it is very reactive and will resinify to a dimer readily. It undergoes addition and condensation reactions with alcohols, phenol, aldehydes and ketones, amines and unsaturated hydrocarbons. Crotonaldehyde is prepared by adding aldol slowly to a boiling, dilute acid and removing the crotonaldehyde, which instantly forms, by distillation.

### Uses

While the greatest use for crotonaldehyde in the United States is for the manufacture of *n*-butyl alcohol, it is also used as a solvent in the purification of oils, in the manufacture of quinaldine and other synthetic organic chemicals and in the manufacture of resins.

### Toxicity

Crotonaldehyde has a pronounced lacrimatory action. It is impossible to remain in an atmosphere of any large amount of the vapor of this substance and prolonged exposure to even low concentrations may result in sensitization. However no serious disabilities have been reported from exposure to this substance in industry. Smyth and Carpenter (1) found the single-dose oral toxicity to rats of crotonaldehyde to be 1 gram per kilogram of body weight and the LD<sub>50</sub> by skin absorption, using guinea pigs, to be 0.03 milliliters per kilogram. The maximum exposure of rats to the saturated vapor with no death was 1 minute. Skog (2) found that on inhalation crotonaldehyde produced the same symptoms as acrolein.

No pronounced peripheral reddening was observed with rats as was the case when crotonaldehyde was administered subcutaneously. Because of its powerful odor and intense lacrimatory effect, crotonaldehyde has been proposed and used as an excellent warning agent in domestic gas for the purpose of detecting leaks (3, 4). It is estimated that when inhaled a concentration of 1 pound of crotonaldehyde in 1 million cubic feet of gas will awaken a sleeping person.

### Analysis

Owing to its aldehyde structure crotonaldehyde should present no particular difficulty in determination where it exists as a single atmospheric contaminant. It may also be identified in micro amounts by conversion to a hydrazone with *p*-nitrophenylhydrazine (5).

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## CYCLOHEXANE

### Characteristics

Cyclohexane, hexamethylene, hexahydrobenzol, C<sub>6</sub>H<sub>12</sub>, molecular weight 84, boiling point 80.80° C., melting point 6.47° C., density *D*<sub>25/4</sub> 0.77388, and index of refraction *n*<sub>25/D</sub> 1.4237, is a colorless, mobile liquid having an odor resembling benzene. It is practically insoluble in water but is miscible with alcohol and olive oil, ether, chlorinated hydrocarbons, and other organic solvents in all proportions. It has a volatility approximately one-third that of ether at room temperature. The flash point is less than zero. It occurs naturally as a constituent in Cau-



casian petroleum and is prepared synthetically by the catalytic hydrogenation of benzene. Cyclohexane is but slightly attacked by sulfuric and nitric acids but dissolves on shaking with 27 parts of fuming sulfuric acid forming sulfonic acid derivatives of benzene. Cyclohexane does not decolorize bromine and when a small amount ( $\frac{1}{2}$  milliliter) is shaken with 2 milliliters of a saturated potassium permanganate solution acidified with sulfuric acid, it shows only slight reduction even after half an hour which serves to differentiate cyclohexane from benzene. Benzene when similarly tested reduces potassium permanganate within 25 minutes.

### Industrial Uses

Cyclohexane probably finds its greatest use in industry as a solvent and it is also employed in chemical manufacture as an intermediate. It is used for the extraction of essential oils in the perfume industry and as a solvent for a variety of fats and oils, as well as paraffin, waxes, and resins. Cyclohexane is used to some extent as a crystallizing medium in the preparation of certain fine chemicals and is also a solvent for synthetic rubber of the neoprene type. It occurs commercially as a constituent of neoprene cements. The production of cyclohexane in the United States amounted to 217,619,000 pounds in 1954.

### Toxicity

Cyclohexane has a weak narcotic effect unaccompanied by clonic convulsions or trembling (Flury). Most authorities agree that cyclohexane is much less toxic than benzene (1). In acute poisoning, the symptoms consist of disturbances in equilibrium, giddiness, and stupor, followed by paralysis of the respiratory center in fatal poisoning. In contrast with benzene, cyclohexane does not cause degeneration of the bone marrow and the blood picture indicates neither anemia nor leucopenia in chronic poisoning. According to Treon and his associates (2), application of cyclohexane to the skin of a rabbit caused irritation and thickening of the skin, but no fatality resulted from repeated cutaneous applications of this sub-

stance. These investigators found that with rabbits exposed to 2.65 milligrams of cyclohexane per liter of air for 50 periods of 6 hours each, there were barely demonstrable microscopic changes in the liver and kidneys. No toxic changes were found in the tissues of rabbits exposed to 1.46 milligram of cyclohexane per liter of air for the same time. According to these investigators, the maximum safe concentration for prolonged exposure of rabbits lies between 434 and 786 parts per million. Fabre and his associates (3) find that rabbits exposed 8 hours per day to atmospheres containing 2.7 to 22 milligrams per liter of cyclohexane showed normal growth curves and no external symptoms of poisoning nor pathological changes. On the basis of their study they recommend cyclohexane as a safe replacement for benzene in industry. Truhaut (4) has pointed out that the presence of benzene as an impurity in commercial cyclohexane does not indicate that cyclohexane itself is toxic.

### Analysis

The concentration of cyclohexane vapor in the atmosphere may be measured by a catalytic type detector or combustible gas indicator. Adsorption on equilibrated activated charcoal (5) is also a useful method. Treon and associates (2) used a combustible gas indicator for concentrations from 0.95 to 2.65 milligrams per liter of air. This indicator has two electrically balanced circuits passing through platinum filaments, one of which is unbalanced by the burning of the hydrocarbons. The extent to which the circuit is unbalanced is a measure of the concentration of cyclohexane. It should be noted that none of these methods, however, is specific for cyclohexane.

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## CYCLOHEXANOL

### Characteristics

Cyclohexanol, hexahydrophenol, hexalin,  $C_6H_{11}OH$ , has a molecular weight of 110, a boiling point of  $161.1^\circ C$ , a melting point of  $25.15^\circ C$ , a density  $D_{30/4}$  of 0.94155, and an index of refraction  $n_{25/D}$  of 1.46477. It is a colorless, oily, viscous, neutral liquid or a colorless, hygroscopic, crystalline solid having a camphor-like odor. It has a vapor density of 3.45, a flash point of  $68^\circ C$ , and is 1/400th as volatile as ether. The solubility in water is 5.4 per cent at  $15^\circ C$  and it is miscible with most organic solvents and oils. Cyclohexanol is produced by the catalytic reduction of phenol by means of a nickel catalyst at  $175^\circ C$ . On oxidation with concentrated nitric acid, cyclohexanol yields adipic acid. Cyclohexanol does not reduce cold aqueous permanganate solution. It is, however, oxidized by a chromic-sulfuric acid mixture yielding cyclohexanone. Cyclohexanol dissolved in concentrated hydrochloric acid at room temperature separates cyclohexyl chloride (boiling point  $143^\circ C$ ).

### Industrial Uses

Cyclohexanol is used as stabilizer, penetrant, blending agent, and homogenizer for various combinations of solvents. It is used in soap making, in the textile industry, in making emulsions, detergents, cutting oils, insecticides, disinfectants, plasticizers, in lacquers, paints and varnishes, and in finish removers. The adipic acid formed on the oxidation of cyclohexanol is useful in chain polymerizations resulting in the formation of methyl rubber or of polychloroprene or by a condensation reaction of the type represented by the synthesis of nylon.

### Toxicity

Pohl (1) was unable to find any other effect than narcosis from feeding or inhalation experiments with cyclohexanol in which cats, rabbits, and dogs were used as experimental animals. No after-effects were apparent in any of these experiments. Narcosis has been noted by Treon and associates (2) as the only sign of intoxication following the oral administration of cyclohexanol to rabbits. However, Sato (3) noted an especially pronounced paralytic effect following the administration of cyclohexanol. When arranged according to lethal dosage by mouth, cyclohexanol falls between cyclohexanone and cyclohexane. Repeated cutaneous application to rabbits produced hypothermia, narcosis, and convulsive movements, although only slight effects are produced with 15 per cent cyclohexanol in potassium oleate. Cyclohexanol (1.09 milligram per liter) causes irritation to the eyes of rabbits. Some narcosis was produced at 4 milligrams per liter, while at 0.58 milligram per liter (145 parts per million) the animals exhibited no evidences of discomfort or intoxication. Nelson and associates (4), in a study of the sensory response to certain industrial solvents, found that cyclohexanol is objectionable to all subjects at 100 parts per million and that at this concentration it causes irritation to the eyes, nose, and throat. According to McConnell (5), cyclohexanol may paralyze the central nervous system and may be more toxic than benzene but is less dangerous owing to its much lower volatility. The maximum allowable concentration of cyclohexanol as reported by various States is between 50 and 100 parts per million.

### Analysis

The concentration of cyclohexanol in air has been determined colorimetrically by Treon and associates (2) by measuring the intensity of the straw color produced by the reaction with catechol and concentrated sulfuric acid. The sample is compared with a suitable standard in a 2-inch cell of a wedge photometer at 520 or 540 millimicrons. The acetyl value (the number of



milligrams of potassium hydroxide required to combine with the acetic acid liberated from 1 gram of acetylated substance) for cyclohexanol is 492.

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### CYCLOHEXANONE

#### Characteristics

Cyclohexanone, pimelic ketone or ketohexamethylene,  $C_6H_{10}O$ , molecular weight 98.1, is an oil with a peppermint-like odor that may be detected in wood spirit oil and together with its homologues in heavy acetone oil. The density is  $d_{20/4}$  0.94653, boiling point  $155.7^\circ C$ ., melting point  $-16.4^\circ C$ ., refractive index  $n_{20/D}$  1.4507, and the flash point  $50^\circ C$ . Its volatility is about 1/40 that of ether. It can be obtained by the oxidation of cyclohexanol or by the catalytic reduction of phenol. Distillation of the salts of pimelic acid yields cyclohexanone. Cyclohexanone dissolves in 27 volumes of water but is salted out by ammonium sulfate. With a saturated aqueous solution of acid sodium sulfite, it yields a sulfite addition compound. When oxidized with warm dilute nitric acid, it reacts violently yielding adipic acid and when reduced with aluminum isopropylate in isopropyl alcohol, it gives cyclohexanol (95 per cent yield).

#### Industrial Uses

Since cyclohexanone on oxidation yields adipic acid, it is useful in chain polymeriza-

tions. This is utilized in the formation of methyl rubber or of polychloroprene or by a condensation reaction of the type illustrated in the synthesis of Nylon. Cyclohexanone is a solvent for cellulose esters and ethers, dyes, resins, lacquers, shellac, oils, and fats. It is used in the textile, lacquer, and leather industries, for metal degreasing, in paint removers, in printing inks, and in the plastics industry.

#### Toxicity

Doubtless, owing to its slight volatility, cyclohexanone is considered to be a comparatively harmless solvent. The experimental work of Specht and his associates (1), however, indicates that animals exposed to 0.4 per cent cyclohexanone vapor for protracted periods show serious after-effects and a certain amount of mortality. In a study of the comparative toxicity of cyclohexanone and a number of related cyclic compounds, it has been found (2) that the minimum lethal dose of cyclohexanone for rabbits by oral administration lies between 1.6 and 1.0 gram per kilogram. While contact with cyclohexanone is characterized by its irritation of mucous surfaces according to some authors. Treon and his associates found that the only sign of intoxication following the oral administration of cyclohexanone was narcosis. They found the maximum safe concentration of cyclohexanone for prolonged exposure of rabbits to be slightly below 190 parts per million. However, it was found by Nelson and his associates (3) that cyclohexanone was not tolerated by man at 50 parts per million, throat irritation being the most marked effect. Twenty-five parts per million was not objectionable to most subjects. Ceresa and Grazioli (4) have found that cyclohexanone administered subcutaneously to guinea pigs is followed by digestive disturbances and anemia. Caujolle and his associates (5) administered cyclohexanone in olive oil intravenously in anesthetized dogs in doses of 0.63 gram per kilogram, and found that this substance is lethal within one hour with symptoms of hypotension and accelerated respiration. All these various

reports indicate therefore a degree of toxicity for cyclohexanone which should receive consideration wherever this substance is used in industry. The majority of the States concur in a maximum allowable concentration value of 100 parts per million for cyclohexanone.

### Analysis

Identification of cyclohexanone may be made by taking advantage of the formation of a number of substances of definite melting point. With hydroxylamine hydrochloride and sodium acetate in dilute methyl alcohol, cyclohexanone oxime (melting point 91° C.) is formed. 1-Methyl-3-carbohydrazidopyridinium *p*-toluenesulfonate (6) gives an easily crystallizable hydrazone having a melting point of 146° C. *p*-Iodobenzohydrazide (7) gives a hydrazone with melting point of 188 to 189° C. A micro-method for the quantitative gravimetric determination has been developed by Sozzi (8) which takes advantage of the precipitation of the yellow crystals formed with 2,4-dinitrophenylhydrazine. Zeidler and Kreis (9) have developed a colorimetric method based upon the violet color given with *o*-nitrobenzaldehyde and alkali in dilute alcoholic solution. The color intensity reaches a maximum after about 1 hour and the rates of maximum color intensity of various cyclic ketones serve to distinguish them. Cyclohexanone as an aerial contaminant may be determined colorimetrically by measuring the intensity of the pink color produced by a reaction of the Zimmerman type, with *m*-dinitrobenzene (2).

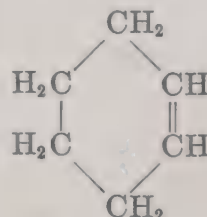
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## CYCLOHEXENE

### Characteristics

Cyclohexene, tetrahydrobenzene, an alkene having the structure



is a colorless liquid having a boiling point of 83° C., a melting point of -103.4° C., density  $d_{20/4}$  of 0.8088, and index of refraction  $n_{20/D}$  of 1.44646. It may be prepared by the dehydration of cyclohexanol with 95 per cent sulfuric acid at 130 to 140° C., by the catalytic dehydration of cyclohexanol with silica gel at 280 to 300° C., or with activated alumina at 380 to 450° C. The latter type of dehydration is accomplished in about 4 hours with a yield of 89 per cent. Cyclohexene adds bromine yielding 1,2-dibromocyclohexane (boiling point 101 to 103° C.) and when dissolved in an inert solvent, such as heptane or xylene, and brominated, it yields cyclohexyl bromide (boiling point 165° C.). When added to a suspension of sodium thiocyanate and copper sulfate in acetic acid and allowed to stand overnight, it forms a thiocyanate addition compound, cyclohexene 1,2-dithiocyanate, which is a white crystalline product melting at 58 to 58.5° C. Cyclohexene is in-



soluble in water but is miscible with alcohol or ether.

### Industrial Uses

Cyclohexene is used as a special solvent and as an intermediate in organic synthesis.

### Toxicity

Lazarew (1) included cyclohexene in a study of the toxicity of various hydrocarbon vapors and found it to be somewhat more toxic than cyclohexane. At a concentration of 30 milligrams per liter, white mice were definitely affected and were killed by concentrations of 45 to 50 milligrams per liter. The reflexes remained positive almost to the point of death. Cyclohexene affected the animals at a concentration of 50 milligrams per liter and death occurred at a concentration of 60 to 70 milligrams per liter. Pohl (2) found that following the inhalation of cyclohexene vapor dogs exhibited symptoms characterized by muscular quivering and reeling or apparent giddiness. Cyclohexene oxide has been patented for use as an insecticidal fumigant (3).

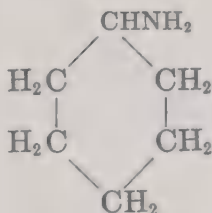
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## CYCLOHEXYLAMINE

### Characteristics

Cyclohexylamine, hexahydroaniline, aminocyclohexane.



is a liquid having a pronounced and disagreeable, fishy odor, an intensely bitter taste and strongly basic properties. It boils at 134.5° C. and solidifies at -17.7° C. Its density is  $d_{25/25}$  0.8647 and index of refraction is  $n_{25/D}$  1.4565. Cyclohexylamine

is completely miscible with water and with most organic solvents. It is prepared by the catalytic hydrogenation of aniline at high temperatures and pressures. The crude reaction product contains unchanged aniline in addition to a high boiling residue of cyclohexylaniline and dicyclohexylamine. Cyclohexylamine is separated from the reaction products by fractional distillation (1).

### Uses

Cyclohexylamine is used in the pharmaceutical industry, in organic synthesis, in the rubber industry, and in dyestuff manufacture.

### Toxicity

In experimental work with animals Watrous and Schulz (2) found that the chief effect of cyclohexylamine vapor appeared to be irritation, which is probably attributable to its strong alkalinity. While the acute lethal dose for rabbits when injected was found to be 0.5 gram per kilogram of body weight, rabbits, guinea pigs and rats were able to survive a daily oral dose of 100 milligrams per kilogram for 82 days, according to Carswell and Morrill (1). Watrous and Schulz (2) cite three cases of industrial exposure. The principal effects noted in these cases were drowsiness and nausea. In one case vomiting occurred. Dilatation of the pupils was noted but pulse and blood pressure were normal. All three cases quickly recovered. Measurement of atmospheric cyclohexylamine concentration when operating under normal conditions indicated that an exposure of from 4 to 10 parts per million caused no symptoms whatsoever in the plant operators.

In three different experiments Watrous and Schulz exposed rabbits, guinea pigs and white mice to cyclohexylamine vapor 7 hours a day to average concentrations of 1,200, 800, and 150 parts per million. Extreme irritation and death occurred at the highest concentration and the vapor caused the corneas of all the animals to become opaque. No convulsant effects were noted at the levels tested. Cyclohexylamine is absorbed through the skin and Mallette and von Hamm (3) found it to be a skin irritant and moderately sensitizing.

## Analysis

The atmospheric concentration of cyclohexylamine vapor may be determined by absorption of the vapor in standardized acid and indirect titration with standardized alkali using bromthymol blue as an indicator. One milliliter of 0.01 N HCl is equivalent to 0.992 milligram of cyclohexylamine (2).

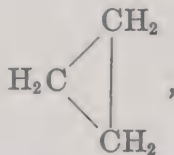
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## CYCLOPROPANE

### Characteristics

Cyclopropane, trimethylene,



an isomer of propylene, is a colorless gas with a characteristic, not unpleasant odor. It boils at  $-34.4^\circ\text{C}$ ., melts at  $-126.6^\circ\text{C}$ ., and liquefies at 4 to 6 atmospheres pressure. While generally stated to be insoluble in water, it is freely soluble in alcohol and ether. It is inflammable and explosive similar to ether. According to Jones and his associates (1), the lower limit of inflammability of cyclopropane in air at room temperature and pressure is 2.45 per cent and the upper limit 10.45 per cent by volume. Cyclopropane has been prepared from trimethylene bromide and sodium or with alcohol and zinc dust or zinc wool with exclusion of moisture. Cyclopropane combines with bromine especially in the presence of hydrobromic acid forming mainly trimethylene bromide. With hydrogen iodide, it forms *n*-propyl iodide. Hydrogen in the presence of finely divided nickel reduces it to propane even at  $80^\circ\text{C}$ .

## Industrial Uses

Production of cyclopropane in the United States in 1945 amounted to 42,000 pounds. By 1953 this had increased to 106,000 pounds annually. It has certain applications in the chemical industry as a starting point in synthesizing various organic substances and has received attention as an inhalation anesthetic, which is said to be characterized by rapid induction and quick recoveries. Cyclopropane will produce narcosis when inhaled in concentrations as low as 4 per cent and the gas may be given by the closed carbon dioxide absorption technique.

## Toxicity

The effects of exposure to cyclopropane are principally those of narcosis, and industrial exposure would be chiefly dangerous from the point of view of inflammability and explosion. Apparently its use as an anesthetic has been limited by the cardiac disturbances which follow this application. Animal experiments with high concentrations of cyclopropane produces arrhythmia with ventricular extrasystoles, followed later by tachycardia and fibrillation. Nausea and vomiting are not frequent nor does the inhalation of the gas cause irritation in clinical concentrations. Seevers and his associates (2) regard its analgesic action as about eight times as great as nitrous oxide and six times that of ethylene. According to Morrison (3), cyclopropane has no discernible postoperative toxic effects on the liver. Evidence is presented by Dripps and Walker (4) to suggest that the hypotension not infrequently noted at the conclusion of cyclopropane anesthesia is related in part to an abnormally high level of carbon dioxide in the arterial blood during anesthesia. This increase in arterial carbon dioxide tension results from the respiratory depressant action of cyclopropane.

## Analysis

No method has apparently been developed for the analysis of air containing cyclopropane as a contaminant. It is possible that in the absence of other combustible constituents, the combustion-indicating apparatus calibrated for cyclopropane itself



could be used. Differentiation between cyclopropane and propylene may be made by taking advantage of the greater reactivity of propylene to an aqueous iodine-bromine solution (5).

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### DIAZOMETHANE

#### Characteristics

Diazomethane, azimethylene,



is a yellow gas with a peculiar musty odor. It is easily condensed to a liquid which boils at  $-23^\circ\text{C}$ . to  $-24^\circ\text{C}$ . The liquid diazomethane, as well as its concentrated solutions, may explode violently on heating, or in contact with the rough surfaces of glass, or particulate matter. In ether or benzene, in either of which diazomethane is readily soluble, the danger of explosion is much decreased, but even the ethereal solution will explode with severe heating. Diazomethane is usually prepared by von Pechmann's original method from methylnitrosourethan. This is a commercial product—a yellowish-red liquid boiling at  $70^\circ\text{C}$ . at 23 millimeters. When this is treated with sodium methoxide, diazomethane is readily evolved. However a number of other methods of preparation have been described, such as the reaction of potassium hydroxide with a chloroform solution of hydrazin and the potassium hydroxide saponification of nitrosomethylurea in ether solution.

#### Uses

Diazomethane is a powerful methylating agent especially useful for the methylating of phenols and carboxylic acids. The reaction is fast, usually quantitative, and can be carried out at room temperature without the addition of other reagents. It is excellent therefore for use with sensitive compounds, as it reacts in neutral solution. While its toxicity and danger have limited its employment in the past, there is an increasing tendency to apply diazomethane in many of the complex and difficult syntheses now demanded of the chemist.

#### Toxicity

Diazomethane is undoubtedly one of the most dangerous products of the chemical laboratory, not only because of its explosive nature, but particularly because of its toxic effects. Since it was discovered in 1894 by von Pechmann, a succession of chemists have drawn attention to its noxious properties. Von Pechmann himself was apparently eventually sensitized against diazomethane. Others have reported irritation of the eyes, dizziness, and denudation of the mucous membranes. In one case vapor from an ethereal solution of diazomethane was found to be severely irritating to the skin, and the fingers became so tender that it was difficult to pick up small objects, such as a pin. Chest pains, fever, and severe asthmatic effects have been reported from contact with the gas. It has been reported furthermore that hypersensitivity results from contact with the substance and further contact brings on attacks of asthma with associated symptoms.

The first case of serious poisoning in the available literature from exposure to diazomethane was reported by Sunderman and his associates (1). In this case a chemist was exposed to diazomethane gas and required 2 weeks of hospitalization before recovery. Severe lung edema resulted from the powerful irritant action of the gas on the mucous membranes of the lungs. LeWinn (2) has recently reported a death from exposure to diazomethane vapor. The victim (also a chemist) was distilling diazomethane under a laboratory hood and inadvert-

ently breathed some of the gas. The effects were not immediate, but began to be apparent on the following day. The symptoms were those of a fulminating pneumonia and the patient died about 100 hours after exposure. At autopsy the gross features were in the respiratory system. Histologic examination of the trachea and main stem bronchi showed the ciliated epithelium to be almost entirely lost and the mucosa thickened by edema and congestion. There was enormous engorgement of the capillaries and small veins. In the lungs there was widespread acute congestion. The pathological diagnosis was acute ulcerative tracheobronchitis, bronchiolitis and bronchiolar pneumonia with secondary changes in the heart, kidney and liver. It does not appear from the reports of these two cases that either of the chemists was careless or exposed to any especially large amount of diazomethane. This all the more points up the deadly character of the substance. Berg (3) has more recently described a somewhat similar case of a worker exposed to diazomethane vapor.

A certain amount of animal experimental work has been reported with reference to diazomethane. Sunderman *et al.* (*loc. cit.*) exposed guinea pigs to the vapor of diazomethane introduced in desiccators and noted the typical asthmatic type of respiration which resulted. Autopsy revealed the pronounced irritant action of the gas on the mucous membranes of the lungs. Flury and Zernik (4) found (with cats as experimental animals) that 175 parts per million of the gas dispersed in 2 per cent ether vapor (diazomethane vapor mixed with air is violently explosive) invariably led to death within 3 days.

In view of the dangerous and insidious nature of diazomethane, it is suggested that it be handled with all the precautions that are adopted in working with arsine, or similar very toxic substances.

### Analysis

Of the several methods that have been adapted to the analysis of diazomethane, that of Marshall and Acree (5) is consid-

ered the best. The diazomethane solution is cooled, treated with 1/10 normal concentration of benzoic acid and after the reaction is complete, the excess benzoic acid is titrated with 1/10 normal concentration of barium hydroxide solution. Other methods consist in adding an excess of iodine and determining the amount used in the reaction, or by adding an alcoholic solution of hydrochloric acid (which reacts to form methyl chloride and nitrogen) and measurement of the amount of nitrogen evolved.

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## DIBUTYL PHTHALATE

### Characteristics

Dibutyl phthalate,  $C_8H_4(COOC_4H_9)_2$ , is a colorless, stable, oily liquid with a boiling point of 340.7° C., density  $D_{20/20}$  of 1.047, vapor pressure of 1.1 millimeter of mercury at 150° C., and an index of refraction  $n_{20/D}$  of 1.4900. It is very slightly soluble in water and is miscible with the common organic solvents. The flash point of dibutyl phthalate lies between 158° and 174° C. It is made by the interaction of normal butyl alcohol and phthalic anhydride. On hydrolysis with alkali, dibutyl phthalate yields *n*-butyl alcohol and phthalic acid.

### Industrial Uses

During 1945, 45,915,000 pounds of dibutyl phthalate was produced in the United States. During the war, this was distributed as follows: 74.6 per cent for the direct use of the military establishment; 6 per cent for synthetic rubber; 4.8 per cent for insect repellants; and 9.3 per cent for plastics, lacquers, cellophane, and adhesives. Smaller amounts were used for photography, textile



coatings, and for cable coatings. Production in 1953 amounted to 23,280,000 pounds. Dibutyl phthalate is used as a plasticizer in nitrocellulose lacquer and in pyroxylin plastics, as a solvent for perfume oils, and, to some extent, as a resin solvent.

### Toxicity

Since dibutyl phthalate does not volatilize readily, the danger from inhalation of vapors would seem to be relatively small. However, plasticizers are often incorporated into synthetic resins by milling upon hot rolls. Shaffer and his associates (1), in making an evaluation of the health hazard of this operation, exposed rats to mists formed by bubbling a stream of air through the plasticizer maintained at 170° C. The data, which give a comparison of the fatal effects in an extremely severe exposure, show dibutyl phthalate to be more dangerous than triethylene glycol di(2-ethylbutyrate), dibutyl sebacate, tricresyl phosphate, or di(2-ethylhexyl)phthalate. In an atmosphere containing 1 milligram per liter of dibutyl phthalate, cats showed irritation of the mucous membranes, salivation, restlessness, irritation of the eyes, and after 3½ hours were exhausted. There was quick recovery and no after-effects (2). It should be pointed out that exposure in these cases was severe. According to Sollmann (3): "No toxic effects, external or internal, have been reported and it is probably harmless". However, toxic nephritis has been reported in the case of a chemical worker who swallowed about 10 grams of dibutyl phthalate by mistake (4). Nausea and giddiness occurred after some hours, his eyes became inflamed and painful with photophobia and lacrimation, and clinical investigation revealed considerable amounts of albumin with many red and white cells in the urine. Under treatment recovery was complete. Inhalation in the form of mist causes throat irritation and since local hydrolysis would produce phthalic acid, it is possible that those individuals who are sensitive to phthalic acid would notice especially irritant effects. No maximum allowable concentration value has been established for dibutyl phthalate.

### Analysis

Owing to its high boiling point, it is unlikely that dibutyl phthalate would be encountered to any extent in ordinary manufacturing operations in the gaseous form. The analytical procedure for the determination of phthalate, according to Smith and Stremper, must be an indirect one since no direct method is satisfactory in aqueous solution. Their evidence indicates that phthalate cannot be determined directly by the addition of lead nitrate or acetate to aqueous solutions containing phthalate ion (5). Dibutyl phthalate mist may be determined in air samples by absorption and hydrolysis with a known amount of standard alkali. Advantage may also be taken of the method adopted for the determination of phthalic anhydride (*q.v.*) as an atmospheric contaminant. The formation of fluorescein with its characteristic powerful green fluorescence is particularly delicate for revealing small amounts of phthalic acid.

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## DICHLOROBENZENE

### Characteristics

*o*-Dichlorobenzene (1,2-),  $C_6H_4Cl_2$ , molecular weight 146.96, one of the three isomeric forms of this substance is a colorless liquid having a boiling point of 179° C.; remains liquid even at -14° C., and has a density of 1.325 at 0° C., a melting point of -18.3° C., flash point 68° C., and index of refraction  $n_{25/D}$  1.5518. Its volatility is about 1/57 that of ether. It is insoluble in water but soluble in alcohol.

*m*-Dichlorobenzene (1,3-) is also a color-

less liquid having a density of 1.307, a boiling point of  $172^{\circ}\text{C}$ ., an index of refraction of  $n_{20/D}$  1.5457, and a melting point of  $-26.4^{\circ}\text{C}$ . It is soluble in alcohol and ether but insoluble in water.

*p*-Dichlorobenzene (1,4-) melts at  $53^{\circ}\text{C}$ ., boils at  $173.7^{\circ}\text{C}$ ., and has a density 1.2675. It is a white solid consisting of monoclinic crystals which are soluble in absolute alcohol and freely soluble in ether, benzene, and carbon disulfide. The refractive index is  $n_{69.9/D}$  1.5266. The relative rate of vaporization was determined by Darkis and associates (1) and the vapor pressure measured by these investigators was found to be 1.02 millimeters of mercury at  $25^{\circ}\text{C}$ . and 8.55 millimeters of mercury at  $50^{\circ}\text{C}$ . As in the case of the other two dichlorobenzenes, *p*-dichlorobenzene is prepared by the further chlorination of monochlorobenzene, *p*-dichlorobenzene being principally formed with the simultaneous formation of only a relatively small amount of *o*-dichlorobenzene. The dichlorobenzenes have an aromatic odor, that of the solid *p*-derivative being penetrating and familiar because of its widespread use.

### Industrial Uses

The extent to which the dichlorobenzenes are used is reflected in the statistical data given by the U. S. Tariff Commission, which states that 15,988,000 pounds of *o*-dichlorobenzene and 34,521,000 pounds of *p*-dichlorobenzene were manufactured in the United States in 1947. *o*-Dichlorobenzene is used as a solvent for gums, fats, oils and waxes, sulfur, resins and lacquers, and in paint and varnish removers, and it is used as an insecticide against the larvae of the crane fly in golf greens and against certain powder post beetles (*Lyctus*). Mixed with glue, it is said to protect cabinet work against wood boring insects. *m*-Dichlorobenzene apparently has no important practical applications. *p*-Dichlorobenzene is familiar as a household insecticide to protect woollens against the clothes moth. Since it was first recommended by Blakeslee (2) as a means of controlling the peach tree borer, *Sannonoidea exitosa* Say, it has been extensively employed for this purpose. It is

also used for the destruction of the sugar cane grub. It has further application as an intermediate in organic syntheses and in drug and dye manufacture.

### Toxicity

As stated by Hunter (3), "The entrance of chlorine into an aliphatic compound increases its toxicity whereas the reverse is the case with an aromatic hydrocarbon. Thus chlorobenzene is less toxic than benzene and causes no trouble in industry." This also applies to the dichlorobenzenes. Consequently the dichlorobenzenes have not proved to be of any great hygienic significance in industry. The few cases of acute poisoning that have been reported are complicated by the fact that the dichlorobenzene was used or applied in a solvent of more distinctive toxic properties, such as carbon tetrachloride. However, a certain amount of injury may follow undue exposure of the skin to these substances on direct contact with the skin. While the danger from the inhalation of the vapor of *p*-dichlorobenzene has been stated to be minimal by such authorities as Flury and Zernik (4) and Lehmann and Flury (5), Berliner (6) cites definite cases of injury following exposure to this vapor. He specifically reports two definite cases of injury in young women resulting from exposure to *p*-dichlorobenzene vapor for periods of 1 or 2 years and refers to cases of injury followed by death of such animals as guinea pigs and rabbits resulting from exposure to the vapor of *p*-dichlorobenzene. Berliner has pointed out the danger of cataract formation and states that in the cases referred to above, the individuals showed jaundice and loss of weight. The formation of cataracts due to exposure to *p*-dichlorobenzene has also been shown to occur by Pike (7). In general, the dichlorobenzenes have a local irritating effect. Following severe exposure, they paralyze the central nervous system and are therefore strongly narcotic and furthermore, they act as metabolic poisons causing liver injury. Cotter (8) has reported several cases of poisoning from *p*-dichlorobenzene with two deaths. The clinical diagnosis was acute yellow atrophy and cirrhosis of the liver



in most of the cases. Cotter has pointed out the danger of exposure to the vapor of this substance and warns against its domestic use. Weller and Crellin (9) report pulmonary granulomatosis following exposure to *p*-dichlorobenzene, and Wallgren (10) cites chronic poisoning of eight workers in a factory producing this substance. No maximum allowable concentration value has been set for *p*-dichlorobenzene. Riedel (11) found that animals painted with *o*-dichlorobenzene became excited and died on the following day. Downing (12) has shown dermatitis to follow from skin contact with *o*-dichlorobenzene and occupational dermatitis has been reported from *o*-dichlorobenzene used in a synthetic varnish (13).

### Analysis

The detection and determination of dichlorobenzene vapor has not heretofore assumed any great importance and therefore no specific methods have been developed for this purpose. General methods, such as freezing the vapor in a tared trap and weighing (1) or the thermal decomposition with quantitative chloride determination by the Volhard method, are suggested procedures.

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## DICHLORODIPHENYLTRICHLOROETHANE (DDT)

### Characteristics

Dichlorodiphenyltrichloroethane (DDT) exists in several isomeric forms depending upon the position of the chlorine substituents. The product resulting from the condensation of monochlorobenzene and chloral, according to the process originally described by Zeidler (1), consists largely of 2,2-bis(*p*-chlorophenyl)-1,1,1-trichloroethane together with the *o* and *p* isomers. Technical DDT is somewhat variable in composition depending on the mode of synthesis. The pure form of DDT melts at 107 to 108° C. DDT is a white powder having a faint, fruity odor and is practically insoluble in water. However, it is readily soluble in a number of organic solvents. DDT is applied either as a dust, in oily solution, or as a mist. In the first case, it is mixed with some inert dust, such as clay, ground soapstone, or talc, in various proportions. If a wetting agent is added, these powders can be mixed with water and used as sprays. Oily solutions are made from various petroleum oils. Aerosols and mists make use of sesame oil, cyclohexanone, or the freons for dispensing agents. Occasionally, dimethyl and dibutyl phthalate or the pyrethrums may be combined with DDT in order to extend its usefulness. The toxic action of the residue of DDT, which persists for some time following its application to insect resting places, constitutes one of the unique advantages of this insecticide.

### Industrial Uses

Since the insecticidal qualities of DDT were reported in 1940 by Müller in Switzerland (2), its applications in this country have increased very greatly. Its efficacy in malarial control has led to the conviction of

many malariologists that malaria eradication is a possibility. It should be pointed out that only the p,p'-DDT isomer is effective against a wide range of injurious insects. Among these are mosquitoes, body lice, houseflies, codling moth, corn borer larvae, and screw worm larvae. The economic importance of DDT is readily apparent when it is considered that damage by the European corn borer larvae in 1945 was estimated at 37 million dollars, that of the screw worm larvae, a serious pest of livestock at 5 million dollars, yearly damage by houseflies at 66 million, and damage by the codling moth larvae to apples and other fruits at about 31 million dollars (3). During 1945, a total of 33,253,000 pounds of DDT was produced in the United States. Annual production had increased to 97,198,000 pounds by 1954.

### Toxicity

Possible harm from DDT may result from its contact with the skin during manufacture, handling the manufactured product in bulk, the preparation of solutions and emulsions, accidental spillage, impregnation of garments with dust or solutions, from absorption through the alimentary canal following the ingestion of contaminated food or water, and through inhalation. While the inhalation of dust is particularly important, skin contact with oily solutions and emulsions also presents a potential hazard. Following its introduction early in the war, many investigations of the toxicity of DDT were made both with reference to its killing power towards insects, as well as its potential danger to man. Fortunately, while DDT is a powerful insecticide and while it can induce toxic features and death if deliberately administered in large amounts, it may be said that it has a wide margin of safety in ordinary manufacture and in use as an insecticide. Even long-continued exposure to concentrations as great as 1 per cent apparently present no danger to man (4, 5). Mackerras and West (6) report an instance in which 25 men ate various amounts of DDT mistaken for baking powder. Within 2½ hours all were weak and giddy. Four vomited but all recovered within 48 hours.

The predominant symptoms in animals resulting from serious poisoning with DDT are muscle tremors and tonic and clonic convulsions. Nervous symptoms and severe damage to the liver are outstanding features. Death may result from central nervous excitation followed by depression and respiratory failure. The usual precautions required in handling toxic substances, such as the early washing of contaminated skin areas with soap and water, the use of gloves and protective garments, and the employment of suitable types of respirators for protection against dust or mist, should be observed. There has been much discussion regarding residuals in foodstuffs following spraying with DDT, particularly since this substance has been found in milk and in human fat (7). Mattson *et al.* (8) examined 50 samples of human fat and found from 2 to 80 parts per million of DDT present in this material. The ultimate effect of this storage of DDT in the fatty tissue and its effect on other organs, notably the liver (9), has received much experimental investigation and discussion. The pronounced effect of DDT on insect life has of course been a matter of especial investigation with particular emphasis on tolerance or resistant insect strains. Vincent and his associates (10) have investigated the toxic mechanism of DDT, both on higher animals and on insects, and have been unable to confirm the theory of anticholinesterase activity ascribed to this substance.

### Analysis

While the usual methods employed for the determination of chlorinated organic substances may be employed for the estimation of DDT as an aerial contaminant, it is quite possible that in manufacturing establishments where the operations of DDT manufacture are dusty, the direct determination of the dust may be effected by physical rather than chemical means. Smith and Stohlman estimated DDT by determining the total chlorine split off by hydrolysis resulting from refluxing in absolute alcohol with metallic sodium followed by titration of the resulting inorganic chloride by the Volhard method (11), Schechter and Haller



have developed a colorimetric method for the determination of DDT based on the blue color formed by the tetranitro-p,p'-DDT derivative (12).

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#### THE DICHLOROETHANES

The structural relationships of the two isomers of dichloroethane (molecular formula  $C_2H_4Cl_2$ ) are shown by the condensed formulas,  $CH_2Cl-CH_2Cl$ , which is 1,2-dichloroethane, or ethylene dichloride and

$CH_3 \cdot CHCl_2$ , which is 1,1-dichloroethane or ethylidene chloride. The first has a boiling point of  $83.7^\circ C$ . and is made when ethylene reacts with chlorine. The latter has a boiling point of  $59.2^\circ C$ . and is prepared by the action of phosphorus pentachloride on acetaldehyde. Since their toxic properties, as well as their physical properties, differ, the two compounds will be discussed separately.

#### 1,2-Dichloroethane

##### Characteristics

1,2-Dichloroethane, ethylene dichloride,  $CH_2Cl \cdot CH_2Cl$ , with boiling point  $83.7^\circ C$ ., melting point  $-35.3^\circ C$ ., density  $d_{20/20}$  1.2554, index of refraction  $n_{20/D}$  1.4443, and molecular weight 98.95, is a colorless liquid with an odor slightly suggestive of chloroform. It is miscible with organic solvents but is soluble in water only to the extent of 0.869 gram in 100 milliliters at  $20^\circ C$ . 1,2-Dichloroethane has a vapor pressure of 62 millimeters of mercury at  $20^\circ C$ . and a flash point of  $15^\circ C$ . It ignites in open flames but does not support combustion.

##### Industrial Uses

1,2-Dichloroethane is an excellent solvent of moderate boiling point. It is used as a solvent for certain synthetic rubbers (Thiokols and Buna N), for oils, fats, waxes, gum and resins, and as an insecticidal fumigant. Occupational exposure to 1,2-dichloroethane occurs among degreasers, dry cleaners, dyers, exterminators, fat and oil extractors, lacquerers, rubber workers, and soap makers.

##### Toxicity

In general, ethylene dichloride, 1,2-dichloroethane, has a narcotic action which is comparable to that of chloroform or of carbon tetrachloride. It is stated to be less toxic than chloroform over short periods of exposure. However, the fatal dose is less than that of chloroform. Exposure to the vapor of this substance causes symptoms of irritation, salivation, and sneezing. The effect on the liver in cases of chronic poisoning has been in dispute. Heppel and his associates (1) have determined the mortality of ani-

mals exposed to various concentrations of 1,2-dichloroethane. Frequent reference in the literature is made to the strong clouding of the cornea which occurs not only as a result of inhalation but even after subcutaneous injection. In an investigation of the effect of various protective agents on rats exposed to 1,2-dichloroethane, Highman and his associates (2) found that the mortality rate and incidence of fatty changes due to exposure to this substance were reduced by the administration of methionine, cysteine, and other sulfhydryl compounds, such as BAL. Hunter (3) cites several cases of industrial poisoning following the inhalation of 1,2-dichloroethane, all of which recovered. However, Brass (4) has reported fatal poisoning in the case of two men repairing a leaking dichloroethane pipe in a pit. They were exposed for 30 minutes before being removed. Both men died, 30 and 33 hours later, with anuria, slight jaundice, and circulatory failure. Greenburg and Moskowitz (5) found that the maximum ethylene dichloride vapor concentration to which any worker should be exposed for the average working day of 8 hours is 100 parts per million.

### 1,1-Dichloroethane

#### Characteristics

1,1-Dichloroethane, ethylidene chloride,  $\text{CH}_3\cdot\text{CHCl}_2$ , molecular weight 98.95, density  $d_{20/4}$  1.174, boiling point  $59.2^\circ\text{C}$ ., melting point  $-96.7^\circ\text{C}$ ., and index of refraction  $n_{20/D}$  1.41655, is a colorless, oily, sweet-smelling liquid having the odor and taste of chloroform. It is prepared by the action of phosphorus pentachloride on aldehyde, or by treating copper acetylide with concentrated hydrochloric acid. 1,1-Dichloroethane is soluble in water to the extent of 5.5 grams per liter at  $20^\circ\text{C}$ .

#### Industrial Uses

1,1-Dichloroethane is a by-product in the manufacture of chloral and is used as an industrial solvent and as an insecticide. It was formerly used as an inhalation anesthetic. 1,1-Dichloroethane is much less used in industry than 1,2-dichloroethane.

#### Toxicity

1,1-Dichloroethane has less narcotic effect than chloroform. There is, however, some danger of chronic poisoning from its use. Lazarew (6) considers this substance to be more toxic than either chloroform or carbon tetrachloride. While some discussion exists regarding the relative toxicities of 1,1-dichloroethane and 1,2-dichloroethane, it does not appear possible at the present time to discriminate between them except on the basis noted above. According to Henderson and Haggard (7), their distinctive odor and irritant properties give warning of their presence in relatively safe concentrations. A maximum allowable concentration of 100 parts per million has been suggested for prolonged exposure (8).

#### Analysis

1,1-Dichloroethane yields a brown color with concentrated sulfuric acid in the cold which differentiates it from 1,2-dichloroethane. In common with other halogenated hydrocarbons, the dichloroethanes present as contaminants in air may be revealed by a flame impinging on a copper strip. In the presence of the halogenated compounds, the flame becomes green or blue colored. The adsorption of the halogenated compounds on activated charcoal or silica gel and the subsequent gain in weight of these substances has been advocated as a method of determination. In its present form, however, this method cannot be recommended as wholly satisfactory. Dudley (9) has described a portable unit for the thermal decomposition and determination of halogenated compounds in general which is useful for the determination of the dichloroethanes as aerial contaminants. Moran (10) has applied this method to the determination of dichloroethane in blood.

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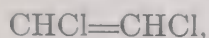


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## DICHLOROETHYLENE

### Characteristics

*sym*-Dichloroethylene, 1,2-dichloroethylene, acetylene dichloride, dioform,



is a colorless, low-boiling liquid with an ethereal, slightly acid odor. The commercial product is a mixture of the *cis* and *trans* forms. The *cis*-form boils at 60.2° C., melts at -80.5° C., has a density of  $d_{15/4}$  1.291, and index of refraction of  $n_{15/D}$  1.4519; while the *trans* form boils at 48.5° C., melts at -50° C., has a density of  $d_{15/4}$  1.265, and index of refraction  $n_{15/D}$  of 1.4490. Commercial dichloroethylene boils at about 55° C. and has a density of about 1.28. Dichloroethylene is insoluble in water but dissolves freely in most organic solvents. It is prepared by the action of chlorine on acetylene when the latter is present in great excess. Industrially, however, it is made by the abstraction of a molecule of chlorine from *sym*-tetrachloroethane by the action of zinc dust. It is rather inert chemically and is noncorrosive to metals in the presence of water. The removal of hydrochloric acid is effected more readily under the action of alcoholic potash from the *cis* form than from the *trans*-isomeride. The hot vapor can be ig-

nited but will not continue to burn unless heat is supplied.

1,2-Dichloroethylene should not be confused with 1,1-dichloroethylene,  $\text{CCl}_2=\text{CH}_2$ , which is known as vinylidene chloride. The vapor toxicity of vinylidene chloride is of the same order as that of dichloroethylene, the flash point is -10° C., and the explosive limit range in air is from 7 to 16 per cent at room temperature (1). Vinylidene chloride should not be stored or handled in the presence of air since the violently explosive peroxide is formed readily when in contact with oxygen. Vinylidene chloride has achieved industrial importance because of its tendency to polymerize, particularly in the presence of benzoyl peroxide. Plasticized and stabilized copolymer compositions of this material are commercially used under the name Saran, which has valuable properties because of its combination of chemical inertness, strength, and toughness.

### Industrial Uses

Dichloroethylene is used for organic syntheses but probably finds its greatest application as an industrial solvent. It is used as a direct solvent for oils, resins, waxes, gums and shellac, and in solvent mixtures for cellulose esters or ethers. As an insecticide, it is much less toxic than ethylene oxide.

### Toxicity

Dichloroethylene is somewhat irritating to mucous surfaces and apparently has a specific irritant action on the cornea of animals. Opinions vary with reference to its narcotic effect, some regarding it as slightly more, others as slightly less than that of chloroform. The concentration necessary to produce narcosis is about 40 milligrams per liter (10,000 parts per million) as given by Wittgenstein (2); according to Lehmann (3), 72 milligrams per liter (18,000 parts per million). The lethal dose likewise is somewhat in dispute. Flury and Zernick (4) indicate concentrations of 155 to 197 milligrams per liter (39,000 to 50,000 parts per million) as the lethal concentration for guinea pigs. The symptoms of poisoning are those of central nervous irritation, as well as narcosis. Restlessness, twitching, and clonic convulsions

have been observed with rapid recovery on removal from exposure. Lacrimation followed by corneal opacity invariably follows narcosis but clears up completely within a day or so following exposure (5). Joachimoglu (6) produced chronic poisoning in animals and found fatty degeneration of the intestinal mucous membrane in addition to loss of weight and the presence of bile pigment in the urine. Although one case of acute poisoning is quoted by Hamilton (7) where a man entered a vat containing rubber dissolved in dichloroethylene and was found dead the next morning, no chronic industrial poisoning has so far been reported. Some slight differences in toxicity between the *cis* and *trans* forms have been found (8); the question, however, is largely academic.

### Analysis

The general methods applicable to the detection and analysis of chlorinated hydrocarbons may be applied to the determination of dichloroethylene vapor in air. The separation of ethylene dichloride and dichloroethylene in mixtures presents some difficulty but a satisfactory procedure has been developed by Winteringham (9) which depends upon the hydrolysis of the mixed chlorides.

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## DICHLOROETHYL ETHER

### Characteristics

Dichloroethyl ether, 1-chloro-2-( $\beta$ -chloroethoxy) ethane, *sym*- or  $\beta, \beta'$ -dichloroethyl ether, Chlorex,  $\text{ClCH}_2\text{—CH}_2\text{—O—CH}_2\text{—CH}_2\text{Cl}$ , is a colorless liquid having a pungent odor, very irritant to the eyes, is practically insoluble in water (1.01 per cent at 20° C.), and is miscible with most organic solvents, but immiscible with the paraffin hydrocarbons. It boils at 178° C., melts at approximately -50° C., has a density  $D_{25/25}$  of 1.210 to 1.220, and a refractive index  $n_{20/D}$  1.457. Dichloroethyl ether is prepared industrially by the chlorination of ethyl ether.

### Industrial Uses

Dichloroethyl ether first recognized as an effective, low-cost solvent, is now being used in other fields, *i.e.*, as an insecticide, soil disinfestant, and as a chemical intermediate. It is a selective solvent for the naphthenic constituents of oils and consequently is widely used by the petroleum industry for certain extracting and refining processes and is also used as an aid in the cleaning of raw wool and cloth. As an intermediate, it is used in the synthesis of such varied products as plasticizers, synthetic rubbers, pharmaceuticals, and resins. In aqueous solution, it is apparently effective as a soil disinfestant against Japanese beetle grubs and wire worms. This substance has proved so useful in the arts and manufactures that publication data, although restricted, indicates that the volume of production is substantially large.

### Toxicity

The chief physiological effect produced in animals and men by dichloroethyl ether is that of irritation. The mucous membranes of the respiratory passages and eyes are predominantly affected. Schrenk, Patty, and Yant (1) determined the acute physiological response of guinea pigs to concentrations of vapor of varying amount and found that owing to its low volatility, it was impracticable to attain a higher concentration for exposure than 0.1 per cent by volume. How-



ever, concentrations of from 0.05 to 0.10 per cent were dangerous to life in from 30 to 60 minutes, while concentrations of from 0.01 to 0.02 per cent were the maximum quantities to which animals could be exposed for 1 hour without serious disturbances. A concentration of 0.0035 per cent by volume produced slight symptoms in guinea pigs after exposure for several hours. In the order of their appearance, the symptoms produced were nasal irritation, eye irritation, lacrimation, respiratory disturbances, dyspnea, gasping, and death. The principal gross pathological findings were congestion, emphysema, edema, and hemorrhage of the lungs. Concentrations of 0.055 and 0.10 per cent of dichloroethyl ether in air produced profuse lacrimation in man on brief exposure. Deep inhalation was nauseating in effect. A lower concentration of 0.0035 per cent of vapor has an easily noticeable odor which is, however, practically free from irritation. The substance therefore possesses definite warning properties in concentrations below those which are dangerous for exposure periods of several hours.

### Analysis

No method of determination specific for dichloroethyl ether as an aerial contaminant has so far been proposed. However, this substance is readily hydrolyzed and methods ordinarily applied to the analysis of organic halogen compounds may be adapted to the determination of dichloroethyl ether in air.

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## DICHLOROMETHANE

### Characteristics

Dichloromethane, methylene chloride,  $\text{CH}_2\text{Cl}_2$ , is a colorless, volatile liquid boiling at  $39.8^\circ\text{C}$ ., melting at  $-96.7^\circ\text{C}$ ., having a density  $d_{20/4}$  of 1.326 (1). The solubility in water is 1.32 gram per 100 grams of water at  $25^\circ\text{C}$ . Its evaporation rate is 71 in com-

parison with that of ether taken as 100. The index of refraction  $n_{20/D}$  is 1.4244. At  $8^\circ\text{C}$ ., its vapor pressure is 200 millimeters of mercury; at  $24.1^\circ\text{C}$ ., 400 millimeters of mercury (2). The ignition temperature is  $642^\circ\text{C}$ . (3), but owing to its low order of flammability the explosive range has not apparently been determined (4). Dichloromethane has wide limits of flammability in pure oxygen. These are 15.5 per cent for the lower limit and 66.4 per cent for the upper limit. Although the method usually referred to for the preparation of dichloromethane is that of partial reduction of the trichloro derivative, chloroform, with zinc and hydrochloric acid, or by the action of phosphorus pentachloride on trioxymethylene, dichloromethane is prepared technically by the chlorination of either methane or methyl chloride.

### Industrial Uses

The manufacture of dichloromethane in the United States has increased considerably and was more than tripled between 1941 and 1946. In the latter year, the production in this country amounted to 13,987,000 pounds. Dichloromethane is used as a refrigerant in air conditioning. In common with many other halogenated hydrocarbons, it has value as a solvent and is used for this purpose for oils, fats and waxes, bitumens, cellulose acetate, and many other organic substances. It is particularly suited for low temperature extraction of materials, such as essential oils and edible fats, which are adversely affected by higher temperatures. It has excellent oil dewaxing properties but, up to the present, has not found extensive use in this field because of its relatively high cost. It is a highly efficient paint remover and is particularly valuable for this purpose because of its nonflammability (1).

### Toxicity

Dichloromethane appears to be one of the least toxic of the chloromethane derivatives. According to Lehmann and Flury, as quoted by Henderson and Haggard (5), the comparative toxicity of dichloromethane with carbon tetrachloride taken as 1, is 0.11. While dichloromethane has a somewhat

more pronounced irritant effect than chloroform, it is a weaker narcotic agent. It had a slight vogue as a general anesthetic and later as an induction anesthetic in Germany under the name "solaesthin". According to Hellwig (6), however, excitation is pronounced and is followed by stertorous breathing, cyanosis, dilated pupils, and a rapid, weak pulse. The relative toxicity on inhalation was determined by Lazarew to be 0.45 for dichloromethane assuming the toxicity of chloroform to be 1 (7). Heppel and his associates (8) found that repeated 7-hour exposures, 5 days a week for 6 months, to 17 milligrams per liter (5,000 parts per million) were tolerated by rats, rabbits, and dogs with no evidence of damage and, except in guinea pigs, with no adverse effect on growth. However, a concentration of 5,000 parts per million of dichloromethane in air causes a great diminution in the running activity of young male rats as measured in a standard type of revolving drum (9). According to Lehmann and Flury (10), dichloromethane is one of the most harmless representatives of the chlorinated hydrocarbon series. A case has been recently reported, however, in which, in a plant engaged in the manufacture of hop extract for brewing, four men were rendered unconscious by the vapor of dichloromethane used in the process. One of the men died from the exposure (11). Moskowitz and Shapiro (12) report four cases, with one death, of men exposed to the vapor of methylene chloride.

### Analysis

Various methods applicable to the analysis of halogenated hydrocarbons may be applied to the determination of the concentration of dichloromethane in air. Since dichloromethane hydrolyzes with water or with a very weak alkali, such as lead hydroxide, to formaldehyde and inorganic chloride, a method based upon determination of either of these substances should be applicable to detection or estimation of the atmospheric concentration of dichloromethane.

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## 2,4-DICHLOROPHENOXYACETIC ACID

### Characteristics and Industrial Uses

2,4-Dichlorophenoxyacetic acid, known as 2,4-D, has come into extensive use within the past 9 years as a plant hormone which kills common lawn weeds, such as dandelion, morning glory, thistle, and burdock, without harming ordinary grass. It is reported to hasten the ripening of fruit and has been used in orchards to prevent the premature dropping of apples. This substance is prepared commercially by causing chloroacetic acid and 2,4-dichlorophenol to react in aqueous alkali or by the direct chlorination of phenoxyacetic acid. Since 2,4-D is a plant hormone, it acts as a plant-growth regulator rather than as a contact poison. In its action on leafy plants, it appears to be absorbed primarily into the epidermal cells, from which it is translocated to various parts of



the plant. 2,4-D induces rapid hydrolysis of starch to sugar and increased respiration (1). The killing of plant tissues is usually a slow process and the killing time may require 2 weeks or even longer. Young vigorous plants are quickly affected and the most efficient herbicidal action occurs when plants are treated in a state of active vegetative growth. Since 2,4-D is not very soluble in water or oil, water-soluble salts or oil-soluble esters prepared in the form of emulsions or dry dust mixtures are used. Water-soluble salt dusts of 2,4-D have been used extensively in rice and sugar cane fields with uniform weed control. During 1945, the first year in which production figures are given for 2,4-dichlorophenoxyacetic acid, 917,000 pounds were prepared in the United States. Annual production had increased to 30,184,000 pounds by 1954.

### Toxicity

Owing to the phenomenal effects of 2,4-dichlorophenoxyacetic acid on weed eradication and the consequent commercial development of this substance as a weed killer, knowledge of its toxicity is important. Workers are exposed to the dust of the sodium or ammonium salts of 2,4-D and to the mist from tributyl phosphate-Diesel oil emulsions in applying this weed eradicator. Further, an important factor in the use of this material is related to residual 2,4-D on plants intended for human or animal consumption. Hill and Carlisle (2) found the LD<sub>50</sub> dose in milligrams per kilogram of 2,4-D by mouth was 375 for mice, 666 for rats, 800 for rabbits and 1000 for guinea pigs. Rats were fed up to 1/10 per cent by weight of their diet over a period of 1 month without any harmful effects. Guinea pigs tolerated 1 gram of the material administered in divided doses of 100 milligrams over a period of 12 days. The experimental work indicated that the mist or clouds of the dry dust of the sodium salt were relatively non-toxic. Mitchell and his associates (3) have shown that no harmful effects on the health or performance of farm animals resulted from the consumption of pasture grass liberally sprayed with 2,4-D. The 2,4-D was not found to be secreted into the milk nor was it found in the blood serum of a calf fed

milk from the cow that received it in her ration. According to experiments conducted by the U. S. Department of Agriculture, one cow received a special dose of about 1/5 of an ounce of 2,4-D daily. Blood samples showed its presence in her circulation but it did not appear in her milk. Mitchell quotes the experimental work of Kraus concerning the ingestion of 500 milligrams of purified 2,4-D per day by a man over a period of 21 days without ill effect. However, the possible presence of poisonous impurities in commercial preparations of 2,4-D should be considered.

### Analysis

Methods for the determination of 2,4-dichlorophenoxyacetic acid have been developed by Rooney (4). These consist essentially in titration of the acid group or, in the case of 2,4-D salts and esters, the conversion to the free acid followed by separation and titration in alcoholic solution. In the absence of other chlorine compounds, oxidation in a Parr bomb may be used, followed by determination of the total chloride. An extremely sensitive colorimetric test for 2,4-dichlorophenoxyacetic acid, or its corresponding salts, consists in gently warming the material with concentrated sulfuric acid and 1,8-dihydroxynaphthalene 3,6-disulfonic acid (chromotropic acid) (5). As little as 0.05 microgram of 2,4-D per milliliter can be detected by this test.

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## 1,2-DICHLOROPROPANE

### Characteristics

1,2-Dichloropropane, propylene dichloride, CH<sub>3</sub>CHClCH<sub>2</sub>Cl, is a colorless liquid

with a chloroform-like odor. It has a density  $d_{20/20}$  of 1.1583, a boiling point of  $96.3^{\circ}\text{C}$ ., a freezing point  $> -70^{\circ}\text{C}$ ., refractive index 1.4340 at  $20^{\circ}\text{C}$ ., vapor pressure of 40 millimeters of mercury at  $20^{\circ}\text{C}$ ., and a flash point of  $21^{\circ}\text{C}$ . Dichloropropane is nearly insoluble in water in which it dissolves only to the extent of 0.26 volume per cent. However, it is miscible with most of the common organic solvents. It is prepared by the action of chlorine on propylene.

### Industrial Uses

Its low water solubility and excellent solvent power for fats, waxes, oils, and grease have made dichloropropane an important commercial solvent. It is used as a solvent in vapor degreasing machines for cleaning metal objects and is also employed in the synthesis of certain pharmaceuticals, plasticizers, and insecticides. The synthetic rubber known as Buna N dissolves in dichloropropane and this material was used in the manufacture of self-sealing gasoline tanks during the war. It has been suggested as an insecticidal fumigant by Hutson (1) and apparently behaves in a manner similar to ethylene dichloride, although it has a much higher boiling point.

### Toxicity

The toxicity of dichloropropane has been investigated by Heppel and his associates (2), who exposed various species of animals simultaneously to known concentrations of this substance. Many deaths occurred among rats, guinea pigs, and rabbits receiving less than eight exposures to 2,200 parts per million of the gas. At a concentration of 1,000 parts per million, deaths occurred among dogs after 24 exposures, among guinea pigs after 22 exposures, and among rats after as few as seven exposures. Animals often showed marked visceral congestion, fatty degeneration of the liver kidney, and, less frequently, the heart, and areas of coagulation necrosis in the liver. According to these investigators, 1,2-dichloropropane is one of the toxic substances to which intermittently exposed laboratory animals may develop increased resistance. The first few exposures cause marked narcosis, whereas subsequent exposures have no apparent narcotic effect

on the animals. This increasing resistance is shown in the pathological picture, for lesions occurring during a series of daily exposures are similar to those following a single exposure and such lesions apparently undergo rapid resolution despite continuation of daily exposures. Hematological studies of exposed dogs and rabbits revealed no abnormalities. These data, in general, indicate that dichloropropane is one of the more toxic of the chlorinated hydrocarbons. The order of increasing lethal action of several hydrocarbons against rats was found as follows: dichloromethane, trichloroethylene, carbon tetrachloride, dichloropropane, and dichloroethane. However, Greenburg and Moskowitz (3), on assigning maximum permissible concentration values for prolonged exposure to solvents used with synthetic rubbers, have suggested 75 parts per million for carbon tetrachloride and 100 parts per million for both ethylene dichloride and propylene dichloride.

### Analysis

The concentration of dichloropropylene in air may be measured by the combustion method of general application to the halogenated hydrocarbons and may be detected by means of a flame detector. It may also be estimated by the general method for the evaluation of solvent vapor content of air by adsorption on air-equilibrated activated charcoal or on silica gel.

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## DIETHYLENE GLYCOL MONOETHYL ETHER AND RELATED SUBSTANCES

### Characteristics

Diethylene glycol monoethyl ether, carbitol, ethyl polyglycol, ethyl diethylene



glycol,  $\text{HOCH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{OC}_2\text{H}_5$ , is a colorless, stable, slightly viscous, hygroscopic liquid having a mild pleasant odor. It has a boiling point of 196 to 198° C., density  $d_{20/20}$  1.023, and an index of refraction  $n_{20/D}$  of 1.4298. It has a freezing point of less than -76° C. and a flash point of 99° C. It is miscible with water and with the common organic solvents and has a sweetish taste followed by a bitter after-taste. When heated at 100° C. with concentrated hydriodic acid, it yields iodine and isopropyl iodide (boiling point 93° C.). The vapor pressure of diethylene glycol monoethyl ether at 20° C. is 0.22 millimeter of mercury. Various esters of diethylene glycol monoethyl ether are commercially important and have the trade names and characteristics given in Table 6.

### Industrial Uses

Carbitol is used in industry as a solvent for nitrocellulose, resins, and dyes. It has application in the preparation of nonaqueous stains for wood and also in the textile industry, where it is used for setting the twist and conditioning yarns and cloth. It is a mutual solvent for mineral oil soap and mineral oil-sulfonated oil mixtures. Many so-called vanishing creams, lotions, and other cosmetic preparations contain this substance as a base and it is also used to some extent in dermatological formulas. Certain carbitol esters, such as the diethylene glycol

monoethyl ether acetate, citrate, laurate, phthalate, and ricinoleate, are used as plasticizers in the plastics industry and as solvents for gums and resins. Diethylene glycol monoethyl ether stearate, which is a cream-colored paste, has waxy properties which make it useful in the polish and textile industries and to some extent in the cosmetic industry.

### Toxicity

The acute toxicity of carbitol has recently been established by Hanzlik and his associates (1) on the basis of various modes of administration at about 6 cubic centimeters per kilogram in rats and mice. To other animals, the  $\text{LD}_{50}$  dose given intravenously was somewhat less. Symptoms were, in general, not demonstrable until more than 1 cubic centimeter per kilogram of diethylene glycol monoethyl ether was administered by any route, including intravenous injection. The intravenous introduction of this substance caused an immediate fall in blood pressure, slowing of the heart, and decrease in kidney volume, which later was followed by a moderately lasting increase. Respiration was invariably depressed. Symptomatically, the acute toxicity of carbitol is characterized by central nervous depression, followed by coma and death. The cause of death in acute poisoning may be respiratory or circulatory failure or both. Circulatory depression is marked following rapid

TABLE 6

Compound	Trade Name	Form and Color	Boiling Point °C.	Melting Point °C.	Specific Gravity	Solubility in Water
Diethylene glycol monoethyl ether acetate	Carbitol acetate	Colorless liquid	217.7	-25	1.0144	Soluble
Diethylene glycol monoethyl ether citrate	Carbitol citrate	Yellow liquid		-16	1.28	Soluble
Diethylene glycol monoethyl ether laurate	Carbitol laurate	Orange semi-solid		19-20	0.94	Insoluble
Diethylene glycol monoethyl ether phthalate	Carbitol phthalate	Pale yellow liquid	235-255 at 4 mm. of Hg	-15	1.121	Slightly soluble
Diethylene glycol monoether ricinoleate	Carbitol ricinoleate	Light amber liquid		-50	0.96	Insoluble
Diethylene glycol monoethyl ether stearate	Carbitol stearate	Cream colored; semi-solid		52-53	0.91	Insoluble

intravenous injection, but respiratory depression is outstanding under all conditions. The acute toxicity of diethylene glycol monoethyl ether was found to be of the same order, but somewhat less than either dioxan or ethylene glycol monoethyl ether, by Laug and his associates (2). Smyth, Seaton, and Fischer (3), in an extended study of the toxicity of glycols and their derivatives, found the LD<sub>50</sub> toxicity of diethylene glycol monoethyl ether, when administered by mouth in single doses, to be somewhat greater than that found by Laug and his associates. Hanzlik and his associates (4) have established the noninjuriousness of diethylene glycol monoethyl ether for, according to their results, continued drinking in medium or low concentrations (1 per cent or less in water) by rats, or eating of high concentrations (5 per cent in food) by mice for nearly two-thirds the life-span of the majority of these animals resulted in slight, negligible, or no impairment of general health. They state that the systemic injuriousness of technical carbitol (carbitol solvent) is largely due to ethylene glycol rather than the diethylene glycol monoethyl ether. In a further study of diethylene glycol monoethyl ether, Hanzlik and his associates (5) have found that single large doses of this substance applied epidermally to rabbits caused acute toxicity and early death. The acute LD<sub>50</sub> was about 8.5 milliliters per kilogram of body weight. Similar applications of other members of the ethylene series, as such, or in mixtures caused death or ill health resembling the chronic intoxication following ingestion.

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### DIETHYL ETHER

#### Characteristics

Diethyl ether or diethyl oxide, commonly called ethyl or sulfuric ether,  $\text{CH}_3\text{—CH}_2\text{—O—CH}_2\text{—CH}_3$ , is a very light, transparent, colorless, volatile, exceeding inflammable, mobile liquid having a pleasant characteristic odor and a burning taste. It boils at 34.60° C., melts at -116.3° C., has a density  $D_{15/4}$  of 0.71925, and an index of refraction of  $n_{20/D}$  1.3526. Its flash point is -41° C. Diethyl ether can be produced from ethanol by distillation with sulfuric acid (the method first discovered by Valerius Cordus in 1540) or by dehydration of ethanol in the presence of aluminum oxide or sulfate catalysts at high pressure and at temperatures of 240 to 260° C. On standing in contact with air, diethyl ether becomes partly oxidized to a nonvolatile peroxide which is left as a residue on evaporation of the solvent and which may explode violently if the distillation is carried out to dryness with overheating. Contact with iron wire inhibits this peroxide formation on standing. At room temperature, water dissolves 7.5 per cent of its volume of ether and ether dissolves 1 to 1.5 per cent of its volume of water. Ether is freely soluble in the ordinary organic solvents. When refluxed with hydriodic acid, diethyl ether yields ethyl iodide (boiling point 72° C.) and when refluxed with 3,5-dinitrobenzoyl chloride in the presence of zinc chloride, it yields ethyl 3,5-dinitrobenzoate (melting point 93° C.).

#### Industrial Uses

Diethyl ether has long been used as an inhalation anesthetic in medicine. It has, however, important industrial uses as a low boiling solvent for fats, oils, and waxes, in the manufacture of nitrocellulose materials, and photographic films, as well as for many minor industrial operations. The industrial



production of ethyl ether in the United States in 1945 amounted to 76,598,000 pounds. In that year, 54.4 per cent was allocated for use in the manufacture of explosives, 12.1 per cent for rubber manufacture, and 8.5 per cent for the manufacture of basic medicinals. Production in 1954 amounted to 56,000,000 pounds.

### Toxicity

The narcotic properties of ether are well known from its use in medicine as an inhalation anesthetic. Ether vapor has an irritating effect on the skin and mucous surfaces to some extent but, in general, ether is less injurious than chloroform inasmuch as its effects are more transitory. The flow of mucus is increased and pneumonia occasionally follows ether anesthesia. Because of the solubility of ether in water, absorption through the lungs occurs with some rapidity. Long-continued inhalation of ether in sufficient concentrations causes death from respiratory paralysis. However, recovery following removal from exposure to non-lethal concentrations is rapid and there are no apparent cumulative or after effects. In certain industries where ether is used, as in the manufacture of smokeless powder from nitrocellulose, chronic effects of exposure to ether vapor have been noted. The symptoms noted are loss of appetite, exhaustion, headaches, sleepiness, dizziness, and psychic disturbances. However, there have been few reports of ill effects in anesthetists exposed daily to ether vapor in concentrations below those producing intoxication (1). It has been stated, furthermore, that some tolerance is built up on repeated exposure to ether vapor similar to the tolerance developed with alcohol.

### Analysis

No very satisfactory specific method for the determination of small amounts of diethyl ether as an aerial contaminant has been devised. It is suggested that in the absence of other organic vapors, adsorption on activated charcoal or on silica gel could be usefully employed for the determination of ether.

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## DI(2-ETHYLHEXYL)PHTHALATE

### Characteristics

Di(2-ethylhexyl)phthalate,  
 $C_8H_4(COOC_8H_{17})_2$

commercially known as Flexol plasticizer DOP, has a specific gravity of 0.986 at 20° C., an index of refraction of 1.484 at 25° C., and a vapor pressure of 0.07 millimeter of mercury at 150° C. It is a light colored fluid which boils at 229° C. under a pressure of 5 millimeters of mercury, melts at < -55° C., has a flash point of 218° C., and is practically insoluble in water, but is miscible with most organic solvents.

### Industrial Uses

Di(2-ethylhexyl)phthalate, often called dioctyl phthalate, is the plasticizer most commonly used with hard vinyl chloride resins to convert them into useful materials with elastomeric characteristics. Di(2-ethylhexyl)phthalate is used for general purpose plasticization and among other things, improves the stiffness (versus temperature) characteristics of vinyl chloride. Copolymers of vinyl chloride and vinylidene chloride, dissolved in methyl ethyl ketone and plasticized with di(2-ethylhexyl)phthalate, are used for molding, extruding, solution coating, impregnating, and film casting (1). Di(2-ethylhexyl)phthalate is used in the production of cable coating compositions and flexible films from various synthetic resins. Production of di(2-ethylhexyl)phthalate in the United States in 1953 amounted to 54,067,000 pounds.

### Toxicity

Shaffer, Carpenter and Smyth (2) have investigated the health hazards involved in the use of di(2-ethylhexyl)phthalate by single dose oral administration, intraperitoneal injection, and inhalation of mist by animals. Since the LD<sub>50</sub> dose (30.7 grams per kilogram) for rats by intraperitoneal administration was the same as that of oral doses,

it appears that absorption of the ester from the digestive tract was no more complete than from the peritoneal cavity. A comparison of the fatal effects upon rats in an extremely severe exposure to the mist of di(2-ethylhexyl)phthalate shows that the health hazards are no greater than those of some other plasticizers in current use without injury to workmen. Since a dosage of 0.4 gram per kilogram per day for 90 days caused no injury to rats beyond somewhat retarded growth, while a dosage of 0.2 gram per kilogram per day caused no injury whatsoever, it may be inferred that di(2-ethylhexyl)phthalate does not possess any great cumulative action. When the plasticizer was applied in the form of patch tests to human skin no erythema or other reaction resulted from either the first or second (sensitization) test. Two men swallowed single doses of 10 grams and 5 grams, respectively. In the former case, this ingestion was accompanied by mild gastric disturbances and moderate catharsis, while in the latter instance no symptoms were noted. In each case, phthalate equivalent to approximately 4.5 per cent of the dose was recovered from the urine in the succeeding 24 hours. The above investigators concluded that di(2-ethylhexyl)phthalate is a chemical substance of low toxicity and that the health hazards involved in its use as a plasticizer are slight. In 1953 Carpenter and his associates (3) investigated the chronic oral toxicity of di(2-ethylhexyl)phthalate over long periods of time and found that rats can tolerate somewhat higher levels than guinea pigs and dogs. The 2-year "no effect" level for rats lies between 0.06 and 0.20 gram per kilogram per day. The 1-year "no effect" for guinea pigs is close to 0.06 gram per kilogram per day; for dogs it approximates 0.06 milliliter per kilogram per day. As a result of this study they feel that "it is reasonable to presume that wide species differences will not be encountered with this plasticizer and that the tolerated level of human intake occurring during industrial handling or resulting from contact of food with packaging materials will not be widely different". Hodge and his associates (4) have recently completed further experimental work with refer-

ence to the chronic oral toxicity of di(2-ethylhexyl)phthalate. When this substance was fed to rats for two years in amounts of 0.1 per cent or less of the diet no detectable effect was observed. Mild toxic changes occurred when a dog was given 5 grams per kilogram daily for 3 months, but no specific histological changes were found in rats maintained on diets containing 0.5 per cent. Hodge concludes that no serious health hazard would be experienced by workers handling this plasticizer and that the minute traces taken up by nonfatty foods packaged in plastics in which di(2-ethylhexyl)phthalate is the plasticizer would be without hygienic significance. No maximum allowable concentration value has apparently been established for di(2-ethylhexyl)phthalate.

### Analysis

The fluorescein reaction provides a convenient method for the estimation of phthalate ester vapor in air (*cf.* Dibutyl Phthalate).

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## DIMETHYLANILINE

### Characteristics

Dimethylaniline, dimethylphenylamine,  $C_6H_5N(CH_3)_2$ , is a yellowish to brownish oily liquid having a boiling point of  $192.5^\circ C.$ , a melting point of  $2.5^\circ C.$ , specific gravity  $D_{20/4}$  0.956, an index of refraction  $n_{20/D}$  1.5582, and a flash point of  $61^\circ C.$  Dimethylaniline is insoluble in water but dissolves freely in alcohol, chloroform, or ether. It is made by heating aniline with methanol and sulfuric acid at a temperature of  $230$  to



235° C. and a pressure of 25 to 30 atmospheres with subsequent treatment with sodium hydroxide. Dimethylaniline is also formed on heating bromo- or iodo-benzene with dimethylamine at 250 to 260° C. Dimethylaniline, in contradistinction with aniline, gives no color with hypochlorites.

### Industrial Uses

The production of dimethylaniline which increased to 18,842,000 pounds in 1942 dropped to 7,041,000 pounds by 1945. Production in the United States in 1954 was 7,017,000 pounds. Early in World War II, it was useful in the synthesis of tetryl, trinitrophenylmethylnitramine. Dimethylaniline is used in other organic syntheses and is especially useful for condensation reactions. With phosgene, it yields tetramethyldiaminobenzophenone (Michler's ketone) and with benzotrichloride, it gives malachite green. It is used in the manufacture of vanillin, methyl violet and other dyes, and as an aid in methylation. Dimethylaniline is a useful analytical reagent for the detection of hydrogen peroxide, hydrogen sulfide, nickel, and nitrites.

### Toxicity

Dimethylaniline has, in general, the same physiological effects as aniline itself. It has a depressing effect on the nervous system and following oral or subcutaneous administration in amounts of 1.2 to 2.5 grams per kilogram of body weight in guinea pigs causes weakness, tremors, tonic and clonic convulsions, slowing of the respiration, and finally death, which is due to respiratory paralysis (1). Watrous (2), in a study of the health hazards of the pharmaceutical industry, found that the hazard when dimethylaniline is used as a solvent in the synthesis of aminopyridine can hardly be overexaggerated. The danger to untrained workers consists of disregarding the presence of small splashes of the oil on their shoes, clothes, or gloves. For trained workers using properly-ventilated equipment, the hazard consists chiefly of accidents in the machinery, with sudden massive exposure to the oil or its vapor. Marked methemoglobinemia was found in several cases in this industry. The princi-

pal industrial hazard found in the United States occurs in connection with the sulfation of dimethylaniline which was an important operation early in World War II. This process resulted in exposure to the vapor of dimethylaniline (3). Enclosure of the sulfation process was recommended and the maximum allowable concentration of dimethylaniline vapor was set at 5 parts per million by the Industrial Hygiene Division of the U. S. Public Health Service. In view of its pronounced toxicity, therefore, exposure to dimethylaniline vapor should be so rigidly controlled in industrial processes that it is minimal.

### Analysis

Since dimethylaniline reacts with nitrous acid to yield *p*-nitrosodimethylaniline which is yellow in color, this procedure may be used for its colorimetric estimation. For this purpose, a set of standards may be prepared and the depth of color used as a basis of quantitative estimation. Haslam and Hearn have used a modification of this procedure for the determination of dimethylaniline in mixtures of aniline, methylaniline, and dimethylaniline (4).

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## DIMETHYLNITROSAMINE

### Characteristics

Dimethylnitrosamine, nitrosodimethyl-

amine,  $\begin{matrix} \text{CH}_3 \\ \diagdown \\ \text{N} \cdot \text{NO} \\ \diagup \\ \text{CH}_3 \end{matrix}$ , is a yellow liquid

having a density of  $d_{20/4}$  1.006, a boiling point of 153° C. per 774 millimeters and an index of refraction of  $n_{20/D}$  1.4364. It is obtained by the addition of very dilute ace-

tic acid and sodium nitrite to a solution of dimethylamine hydrochloride. The dimethylnitrosamine separates as a yellowish, oily liquid which is volatile with steam and may thus be separated. When reduced in alcoholic solution by means of zinc dust and acetic acid it is converted to dimethylhydrazine.

### Uses

Dimethylnitrosamine is an intermediate used in synthetic reactions and is used industrially in the manufacture of dimethylhydrazine.

### Toxicity

According to O'Leary and his associates (1) dimethylnitrosamine causes illness in workers exposed to it. Experimental work with animals has indicated that this substance causes liver damage. In mice the LD<sub>50</sub> was found to be 16.5 milligrams per kilogram of body weight when administered either intravenously or intraperitoneally. With rabbits the LD<sub>50</sub> was lower and more irregular. Toxic doses in mice, rabbits, and dogs caused no immediate outward signs, but lethargy, coma, and death occurred after 12 hours to 4 days. The predominating changes found on postmortem examination were bloody ascites, fluid in the chest, and enlarged or discolored livers. However no significant changes were noted in animals that had survived acute dosages.

### Analysis

No specific method has been developed for the determination of dimethylnitrosamine as an atmospheric contaminant. A suggested procedure is based on the nitrosamine test of Liebermann. When phenol is added to nitrosamine followed by sulfuric acid a dark-green solution is obtained that turns red when diluted with about 10 volumes of water. If this solution is then made alkaline, a very deep blue solution is obtained.

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## DIMETHYL SULFATE

### Characteristics

Dimethyl sulfate,  $(\text{CH}_3)_2\text{SO}_4$ , is a colorless, oily liquid, boiling at 188° C. and having a specific gravity of 1.3516. It solidifies at -27° C. and has an index of refraction of  $n_{20/D}$  1.3874. Dimethyl sulfate is almost insoluble in water but undergoes hydrolysis in contact with it. It is miscible with alcohol and ether. The vapor of dimethyl sulfate is 4.4 times heavier than air and has a faint odor of onions. At ordinary temperature (20° C.), its volatility is low and amounts to only 3.3 milligrams per liter. The vapor is readily decomposed by moist air yielding methyl alcohol and sulfuric acid. The ester is conveniently prepared by the interaction of methyl alcohol and chlorosulfonic acid with distillation under reduced pressure.

### Industrial Uses

Dimethyl sulfate is a methylating agent used in the manufacture of many organic chemicals, such as methyl ethers, esters, and amines. During World War I, this substance was used as a war gas, first by the Germans in August 1915 under the name "D-Stoff" and later by the French (in September, 1918) as "Rationite" in artillery shells and hand grenades. Apart from its manufacture in the chemical industry, dimethyl sulfate is specifically used in perfume, dye, and color manufacture.

### Toxicity

Dimethyl sulfate has long been recognized as a distinctly poisonous substance. It is not only a severe systemic poison following oral administration exhibiting pronounced effects on the central nervous system (somnolence, convulsions, delirium, coma, paralysis), and a powerful irritant following inhalation, but the liquid causes immediate symptoms of irritation following skin contact. The lesions produced by splashes of the liquid on the skin vary with the duration of contact and much resemble sulfuric acid burns, except that the burns require a longer time to heal. The eyes are painfully affected following exposure to dimethyl sulfate, as the substance is a powerful lacrimator. It is



generally assumed that dimethyl sulfate exerts its toxic action due to its local hydrolysis to methanol and sulfuric acid at the cell site. This probably explains its pronounced toxic action following inhalation. However, certain toxic manifestations of the substance have been attributed to the molecular substance itself rather than to its hydrolytic products. Working with dimethyl sulfate is particularly hazardous because of the absence of any warning sign, such as odor, and also due to the latent period without symptoms. The onset of clinical symptoms may be delayed as long as several hours. In this respect, the action of dimethyl sulfate is comparable to that of phosgene. In fact, continuous chronic intake of small sublethal doses results in a cachectic condition similar to that of phosgene poisoning. Merkelbach (1) differentiates clinically the following changes: a) local necrotizing corrosions, b) corrosion of the air passages by vapors, and c) toxic impairment of kidneys, liver, and focal areas of fatty degeneration in the myocardium. Numerous cases (2, 3, 4, 5) of dimethyl sulfate injury have occurred in industry, several of which terminated fatally. Littler and McConnell (6) have reported two cases of dimethyl sulfate poisoning and stress the value of oxygen and antibiotics in its treatment.

### Analysis

The determination of small amounts of dimethyl sulfate vapor in air may be made by absorption in alcoholic potassium hydroxide solution, completing the hydrolysis and precipitating the sulfate as barium sulfate. A turbidimetric or nephelometric procedure based on barium sulfate may also be used for very small amounts.

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## DINITROBENZENE

### Characteristics

Dinitrobenzene,  $C_6H_4(NO_2)_2$ , is a solid at ordinary temperatures and in the pure state forms colorless crystals. The introduction of a second nitro-group into nitrobenzene may yield three isomers, *o*-, *m*-, and *p*-dinitrobenzene. *o*-Dinitrobenzene, 1,2-dinitrobenzene, boils at 319° C., melts at 117.9° C., and has a density of 1.546. *m*-Dinitrobenzene, 1,3-dinitrobenzene, boils at 302.8° C., melts at 89.9° C., and has a density of 1.546. *p*-Dinitrobenzene, 1,4-dinitrobenzene, boils at 299° C., melts at 172° C., and has a density of 1.587. Of the three isomers, *m*-dinitrobenzene only is of commercial importance. The *m*-dinitrobenzene is but slightly soluble in cold water, more soluble in boiling water, soluble in alcohol, chloroform, and ethyl acetate, and soluble in benzene to the extent of 39.5 parts per 100 at 18° C. It is obtained by a second nitration of mononitrobenzene using sulfuric and fuming nitric acid. This second nitro-group entering the benzene ring is directed chiefly into the *meta*-position although 7 to 10 per cent of *o*- and *p*-dinitrobenzene are formed. These may be removed by washing. Since *m*-dinitrobenzene is the simplest of the dinitrobenzenes to manufacture, it is the one most commonly used in industry.

### Industrial Uses

In 1941, the last year for which figures are at present available, 3,287,000 pounds of dinitrobenzene was made in the United States. *m*-Dinitrobenzene is used extensively in the dye industry and in the explosives industry. Lesser uses are in organic synthesis and to some extent in the plastics industry.

### Toxicity

Since dinitrobenzene is a solid, cases of poisoning develop less rapidly and are less severe than in the case of mononitrobenzene (1). Poisoning occurs among men who either shovel or melt dinitrobenzene. An attack

usually develops some hours after a man has left the plant. The main physiological effect of dinitrobenzene is the conversion of oxyhemoglobin into methemoglobin. This may progress to the extent of making the blood a chocolate color. The red cells are reduced in numbers and show marked punctate basophilia. Dinitrobenzene is changed into *m*-nitroaniline and is eliminated in this form in the urine. A workman may notice that he passes smoky urine soon after his first contact with dinitrobenzene. In acute poisoning, there is a rapid onset of headache, vertigo, and vomiting, followed by exhaustion, numbness of the legs, a staggering gait, somnolence, and loss of consciousness. In subacute and chronic poisoning, secondary anemia is a prominent feature. As with mononitrobenzene, working garments, gloves, and boots must be changed and cleaned regularly. Absorption from the alimentary canal is more rapid if the stomach is empty which makes it desirable that workers eat a meal before they begin work. Alcohol used even in ordinary amounts increases the toxic effects of dinitrobenzene. The literature concerning the toxicity of dinitrobenzene has been reviewed by von Oettingen (1) and critically evaluated by Hunter (2). Kiese (3) has studied both acute and chronic poisoning of dogs with *m*-dinitrobenzene administered subcutaneously. The median lethal dose was 10 milligrams per kilogram. The formation of Heinz bodies, an increase in methemoglobin, and liver damage was noted both in acute and in chronic poisoning. As yet no maximum allowable concentration for this substance has been established.

### Analysis

The three dinitrobenzenes are volatile with steam and may be separated by this means for purposes of identification. *o*-Dinitrobenzene, on treatment with ammonium sulfide in alcohol or on boiling with ammonia in alcohol, yields *o*-nitroaniline (melting point 71° C.). When reduced by tin and hydrochloric acid, it yields *o*-phenylenediamine (melting point 102° C.). With aniline at 100° C., it yields *o*-nitrodiphenylamine (melting point 75° C.). *m*-Dinitrobenzene,

when similarly treated to the above, yields *m*-nitroaniline (melting point 114° C.) and *m*-phenylenediamine (melting point 63° C.). *p*-Dinitrobenzene yields respectively *p*-nitroaniline (melting point 147° C.) and on reduction, yields *p*-phenylenediamine (melting point 140° C.). *m*-Dinitroaniline as an aerial contaminant may be determined directly by the colorimetric method with ketones, such as acetone, methyl propyl ketone, etc., which form violet colors, the intensities of which are proportional to the *m*-dinitrobenzene concentration (cf. Benzene).

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## DINITRO-*o*-CRESOL

### Characteristics

Dinitro-*o*-cresol, 3,5-dinitro-2-oxymethylbenzene, 2-methyl-4,6-dinitrophenol, (NO<sub>2</sub>)<sub>2</sub>C<sub>6</sub>H<sub>2</sub>(CH<sub>3</sub>)OH, crystallizes as yellow prisms from alcohol and has a melting point of 85.8° C. It is prepared by treating *o*-cresol in glacial acetic acid with nitric acid in the cold, or by sulfonation of *o*-cresol followed by controlled nitration. Dinitro-*o*-cresol is moderately volatile with steam. On heating with sulfur and alkali sulfides a black, direct cotton dyestuff is formed. Wain (1) found the solubility of dinitro-*o*-cresol in various solvents (grams dissolved by 100 grams of solvent at 15° C.) to be as follows: petroleum ether 0.51; carbon tetrachloride 2.40; ethanol 4.30; methanol 7.33; diethyl ether 9.12; glacial acetic acid 23.45; benzene 37.15; chloroform 37.20; and acetone 100.60. One part of dinitro-*o*-cresol dissolves in 7,813 parts of water at 15° C.

### Uses

The following salts of dinitro-*o*-cresol are found in commercial use: the sodium salts,



$\text{NaC}_7\text{H}_5\text{N}_2\text{O}_5$ , a red powder, and the hydrate  $\text{NaC}_7\text{H}_5\text{N}_2\text{O}_5 \cdot \text{H}_2\text{O}$ , yellow needles; the ammonium salt  $\text{NH}_4\text{C}_7\text{H}_5\text{N}_2\text{O}_5 \cdot \text{H}_2\text{O}$ ; the potassium salt  $\text{KC}_7\text{H}_5\text{N}_2\text{O}_5$ ; and the calcium salt  $\text{Ca}(\text{C}_7\text{H}_5\text{N}_2\text{O}_5)_2 \cdot \text{H}_2\text{O}$ . All these salts are readily soluble in water. In the form of solutions of its salts, it has been known as an insecticide under the name of "Antinonin" in Germany and "DNOC" in England. As a crop spray dinitro-*o*-cresol was introduced into this country about 1940. It is also used as a weed killer and fungicide. While the amount manufactured in this country is not great in comparison with other insecticides or herbicides, the output in 1948 amounted to 202,000 pounds.

### Toxicity

Dinitro-*o*-cresol is markedly toxic and has been the cause of illness and fatalities both in its manufacture and agricultural application. To some extent this substance has been used by overweight individuals to produce loss of weight. Several fatalities have been reported from this application in England and in Germany (2, 3). The symptoms of poisoning are a particularly marked thirst, perspiration, increased temperature, and increased pulse and respiration rate (4). In severe poisoning the symptoms are dizziness, restlessness, vomiting, intense perspiration, fever and unconsciousness. However, stimulation of the metabolism, hyperthermia, profuse sweating and general malaise characterize poisoning in general by dinitro-*o*-cresol; furthermore, loss of weight, glaucoma, bilateral cataract, and painful erythema of the hands may follow contact with this substance (5).

Ambrose (6) found that the 3,5 isomer was not fatal when administered orally to rats in amounts of 30 milligrams per kilogram of body weight, or with 20 milligrams per kilogram following subcutaneous injection, while 50 to 100 milligrams per kilogram administered by mouth was 100 per cent fatal. The "survival dose" following oral administration was found by Spencer and others (7) to be 10 milligrams per kilogram for rats, while the lethal dose was 50 milligrams per kilogram. Parker and others (8) found the  $\text{LD}_{50}$  in rats by subcutaneous in-

jection to be approximately 24.6 milligrams per kilogram of body weight.

Nordmann and Weber (9) report a yellow coloration of the skin and of the respiratory tract to be particularly noticeable. Furthermore, cloudy swelling of the kidneys and liver was noted in this investigation. Spencer (7) also reports cloudy swelling of the liver, very slight degenerative changes in the renal tubules, and slight congestion of the spleen in rats fed a diet containing 0.10 per cent of 4,6-dinitro-*o*-cresol. However in the more recent investigation of Parker and others (8) no signs of cellular damage were found in the livers of animals killed or dying after either single or repeated injection of dinitro-*o*-cresol. They found that a single dose approximating a lethal dose produces an acute reaction lasting a few hours, but that a sublethal dose may be administered at daily intervals for several weeks without producing symptoms or signs of chronic poisoning. There are therefore apparently no accumulative effects in rats, nor is any tolerance developed towards dinitro-*o*-cresol. In the case of a man poisoned with this substance, reported by Pollard and Filbee (4), the blood level concentration of 60 micrograms per gram of blood of the patient on admission to the hospital was dangerously near that reported by Steer (10) of 75 micrograms per gram of blood in a fatal case of poisoning from dinitro-*o*-cresol. The extreme muscular rigidity at or very soon after death in poisoning with dinitro-*o*-cresol has been attributed to depletion of energy-rich phosphate compounds in tissues and organs by Parker (11). The main detoxication mechanism is that of reduction of the 6-nitro group and not conjugation of the phenol group. The main detoxication product is 6-acetamido-4-nitro-*o*-cresol which is far less toxic than dinitro-*o*-cresol (12).

Inhalation of the dust of dinitro-*o*-cresol has been the cause of illness and deaths. For instance, Schwartz (13) reports the death of a worker from this type of exposure. Couchman (14) reported the first case of industrial poisoning (with recovery) from exposure to dinitro-*o*-cresol dust in this country. The worker so exposed had been working in a plant where the atmospheric contamina-

tion amounted to 4.7 milligrams of the substance per cubic meter of workroom air. This individual was admitted to the hospital with a temperature of 102° F., a basal metabolic rate of 400+, rapid pulse and respiration, profuse sweating, shortness of breath and cough. The skin on the palms of the hands and soles of the feet was colored canary yellow. Satisfactory working conditions were attained when the process was so modified as to permit exposure to no more than 2.5 milligrams per cubic meter of air. Bidstrup and Payne (15) discuss nine fatal cases of dinitro-*o*-cresol poisoning which have occurred in Great Britain since 1945. In all except one of these cases the men had been working less than 12 hours before death. Owing to increase in the metabolic rate, death may occur through heat stroke and usually occurs in hot weather within a few hours after the appearance of symptoms. In man it apparently acts as an accumulative poison and is the more dangerous on that account (Harvey, Bidstrup and Bonnel, 16). Fischer (17) has made recommendations for the safe application of dinitro-*o*-cresol. Pollard and Filbee (4) recommend that all people exposed to dinitro-*o*-cresol should have regular blood examinations and should avoid contact with the substance for several weeks if their blood content of this substance rises above 20 micrograms per gram of blood.

### Analysis

The yellow color of an aqueous solution of dinitro-*o*-cresol is discharged by the addition of hydrochloric acid, while the addition of an aqueous solution of ferric chloride to an alcoholic solution of this substance develops a yellow to deep red color. When warmed with a solution of sodium hypochlorite, chloropicrin is formed and may be recognized by its acrid odor. According to Wain (1) dinitro-*o*-cresol is sufficiently acidic to liberate iodine from an iodate solution. The liberated iodine can be titrated preferably by the addition of excess thiosulfate followed by back titration. A colorimetric method of analysis, especially suitable for the analysis of insecticidal material, has been developed by Fischer (17). The latter is digested with 1 per cent NaOH, filtered, neutralized with sulfuric acid, and treated

with a freshly prepared solution of potassium cyanide. A deeply colored "purpurate" is formed thereby which may be measured colorimetrically.

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## DINITROPHENOL

### Characteristics

Dinitrophenol,  $C_6H_5OH(NO_2)_2$ , exists in six isomeric forms, the physical properties of which are summarized in Table 7. As ordi-



narily prepared dinitrophenol consists of mixtures of the various isomers and, except for special purposes, the mixture is used without separation of the isomers.

### Uses

Formerly the most important use for dinitrophenol was as an explosive. When mixed with picric acid it constituted the French explosive mélinite. However it is now largely used in the synthesis of dyestuffs and as a wood preservative. 2,4-Dinitrophenol on reduction with iron and hydrochloric acid

yields diaminophenol, a photographic developer known commercially as Amidol.

### Toxicity

There is a considerable amount of variation in the toxicity of the various isomeric dinitrophenols, but the 2,4 derivative is by far the most toxic of the entire group. During 1915 and 1916 numerous cases of dinitrophenol poisoning occurred in France in the filling of shells with mélinite. Twenty-seven deaths were reported arising from dinitrophenol poisoning. While absorption occurs to

TABLE 7

Isomeric Forms of Dinitrophenol	Characteristics					
	Melting point	Boiling point	Density	Physical state	Solubility	Remarks
	<i>degrees C.</i>					
2,3-Dinitrophenol	144	dec.	1.681 at 25°	Yellow needles when crystallized from water	Very easily soluble in ether and hot alcohol	
2,4-Dinitrophenol	114–115	dec.	1.683 at 24°	Thin, nearly colorless plates when crystallized from water	Easily soluble in warm ether, benzene, or chloroform	Volatile with steam
2,5-Dinitrophenol	104			Slightly yellow needles when crystallized from water, dilute alcohol, or ligroin	Difficultly soluble in water, cold alcohol; readily soluble in hot alcohol or ether	
3,4-Dinitrophenol	134	dec.	1.672	Colorless needles from water which soon disintegrate to a sand	Easily soluble in alcohol or ether	Not volatile with steam
3,5-Dinitrophenol	122	dec.	1.702	Colorless plates from dilute HCl solution	Very easily soluble in alcohol or ether; difficultly soluble in petroleum ether	
2,6-Dinitrophenol	63.5	dec.		Yellow rhombic crystals	Slightly soluble in cold water; more soluble in hot water; readily soluble in hot alcohol; soluble in benzene and in ether	

some extent through the respiratory tract and to a less extent from the alimentary tract, the principal industrial hazard is absorption through the skin. Workmen show staining of exposed surfaces, and the hands and soles particularly exhibit yellow staining.

A number of years ago it was discovered that dinitrophenol causes a marked increase in metabolic rate and a rise in temperature. In 1933 Cutting and his associates (1) used dinitrophenol in treating obesity and for a time this treatment enjoyed considerable vogue. However the severe and occasional fatal effects attending its use shortly terminated its popularity. In addition to the effects noted above, dinitrophenol produces extreme weariness, profuse sweating, burning thirst, dyspnea, collapse and death. With non-fatal poisoning the symptoms improve on removal of the victim from further contact with dinitrophenol. Where this substance had been used as a drug for some time, it was found that cataract formation was a late complication.

Simon (2), in his study of the mechanism of dinitrophenol poisoning, found that this substance stimulates glycolysis and inhibits oxidative phosphorylation, which in turn inhibits processes requiring energy. It also causes a loss of reservoirs of energy-rich phosphate. Fonnesu and Severi (3) have found that in rats prolonged treatment with 2,4-dinitrophenol causes at first an accumulation of liver glycogen which later on disappears completely. Fasting rats similarly treated have a higher blood sugar level and less glucose tolerance. Chronically poisoned rats show liver changes, kidney swelling, and necroses (4). According to Williams (5) 2,4-dinitrophenol is excreted partly unchanged, partly conjugated with glucuronic acid, and partly reduced to 2-amino-4-nitro-, 2-nitro-4-amino-, and probably 2,4-diaminophenols.

While the majority of reports concerning industrial injury originated in the munitions industry, Saita (6) reports occupational poisoning among workers impregnating wood with dinitrophenol. In industry adequate ventilation should be provided to remove dinitrophenol present as dust and, since skin absorption is the principal portal of entry,

special attention should be directed to washing and change of clothing.

### Analysis

The many color reactions of the nitro group facilitate the identification and determination of these substances by colorimetry or absorption spectrophotometry. The dinitrophenols are important indicators for changes in pH, the color changing from colorless to yellow with 2,4-dinitrophenol at 2.0 to 4.7; with 2,6-dinitrophenol at 1.7 to 4.4; and with 2,5-dinitrophenol at 4.0 to 6.0. Since dinitrophenol is excreted partly unchanged and partly reduced the Derrien test may be applied to the urine in cases of suspected dinitrophenol absorption (7). This test is especially sensitive for aminonitrophenol.

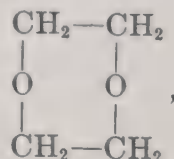
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## 1,4-DIOXANE

### Characteristics

1,4-Dioxane, 1,4-diethylene dioxide, 1,4-diethylene ether, the second ether of ethyl-



ene glycol, is a colorless liquid with a faint, pleasant, ethereal odor. It boils at 101.4° C., melts at 11.8° C., has a density  $d_{20/4}$  of 1.03361, and an index of refraction  $n_{20/D}$  of 1.4232. It is miscible in all proportions with water and the ordinary organic solvents. The vapor pressure at 20° C. is 29.0 millimeters of mercury and the flash point is 5° C. It forms a constant boiling mixture, 80 per cent



dioxane and 20 per cent water, with a boiling point  $86.8^{\circ}$  to  $86.9^{\circ}$  C. at 742 millimeters of mercury. It is quite stable and is little affected by acids, alkalies, or oxidizing agents at ordinary temperatures (1). Commercial dioxane is likely to contain as impurities ethylene acetal, acetaldehyde, water, and dioxane peroxide. The lower flammable limit of dioxane vapor in dry air at ordinary laboratory temperature and pressure is 1.97 per cent by volume, the upper limit at laboratory pressure and  $100$  to  $110^{\circ}$  C. is 22.25 per cent by volume. Dioxane is prepared by the polymerization of ethylene oxide or by the distillation of glycol with dilute sulfuric acid.

### Industrial Uses

Dioxane is used as a solvent in the textile, lacquer, and celluloid industries. It is used as a degreaser, especially for wool, in the manufacture of cosmetic and pharmaceutical preparations, as a preservative, fumigant or deodorant, as a paint remover, and in the manufacture of polishes, pastes, glues, adhesives, emulsions, and cleaning preparations. It also has a number of minor uses, such as its employment in histological laboratories and as a solvent for certain spirit-soluble dyes.

### Toxicity

Yant *et al.*, (2), following the exposure of guinea pigs to dioxane vapor for a short period of time, found that this substance acted as a mild lung irritant, but they were unable to demonstrate other outstanding pathology. Persons exposed to 0.16 per cent in air by volume immediately experienced a slight irritation of the eyes and nose, and exposure to 0.55 per cent produced more marked symptoms with the addition of a burning sensation in the throat. These investigators concluded that the local irritating action would provide warning at a point far below that causing a health hazard from breathing the vapor. However, Fairley and his associates (3), after repeated inhalation experiments on animals, found that injury to the kidneys and liver was produced by repeated exposure to nonfatal doses of 0.1 and 0.2 per cent vapor by volume and by ab-

sorption through the skin. Lehmann and Flury (4) exposed animals to 10 milligrams per liter (0.27 volume per cent) daily for 8 hours. Though 7 of the 10 exposed animals died, the remainder withstood 34 additional exposures. When dissected, all animals showed liver and kidney injury. Barber in 1934, according to Hunter (5), reported the death of five men from exposure to dioxane in the manufacture of artificial silk. Severe gastric symptoms, liver enlargement, anuria, and uremic coma developed. Autopsy revealed hemorrhagic nephritis and necrosis of the liver. While the process on which they were employed had been in use for nearly 16 months, the circumstances were such that the deaths were attributed to a few intense exposures and not to chronic poisoning. The early diagnostic signs include irritation of the nasopharynx and eyes, drowsiness, vertigo, headache, loss of appetite and nausea as well as an increase in the number of leucocytes (6). Hunter suggests that where the use of dioxane cannot be confined to enclosed apparatus, adequate exhaust ventilation must be provided and large evaporation surfaces forbidden.

### Analysis

For the measurement of concentrations of dioxane as an aerial contaminant, Schrenk and Yant (6) employed activated charcoal and determined its gain in weight following passage of air through this material. While no direct chemical method for the determination of dioxane has been developed, it is suggested that since dioxane has an oxidizing effect on iodides and its liberation of iodine has been made the basis of the detection and determination of small amounts of iodides (7), a reverse procedure could be employed for the estimation of dioxane vapor either directly or following concentration by trapping.

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## DIPHENYL AND ITS AMINO AND NITRO DERIVATIVES

### Characteristics and Industrial Uses

Diphenyl,  $C_6H_5C_6H_5$ , is a crystalline colorless substance having a pleasant odor. Its specific gravity is variously given as 0.9845 to 1.041, its melting point is  $70.5^\circ C$ ., and its boiling point is  $254^\circ C$ . It is insoluble in water but soluble in alcohol and ether. Diphenyl is prepared by passing benzene vapor through an iron tube packed with pumice held at a relatively high temperature ( $650^\circ$  to  $800^\circ C$ .). It may also be prepared by passing the vapor through molten lead. Diphenyl is used as a heat-transfer fluid in a commercial preparation known as Dowtherm A, which is an eutectic mixture containing 26.5 per cent of diphenyl and 73.5 per cent of diphenyl oxide. Diphenyl is also used in organic synthesis.

The aminodiphenyls may be prepared by the reduction of the corresponding nitro compounds. *o*-(2)-Aminodiphenyl may be produced by the action of bromine and an alkali on *o*-phenylbenzamide. It has a melting point of  $49^\circ C$ . *p*-(4)-Aminodiphenyl, xenylamine, may be prepared by the interaction of benzene with azobenzene hydrochloride in the presence of aluminum chloride. The melting point of the para compound is  $54^\circ C$ .

When diphenyl is nitrated, a mixture of *o*-nitrodiphenyl and *p*-nitrodiphenyl is obtained. *o*-(2)-Nitrodiphenyl melts at  $37^\circ C$ . and boils at  $320^\circ C$ .; *p*-(4)-nitrodiphenyl melts at  $114^\circ C$ . and boils at  $340^\circ C$ .

### Toxicity

When absorbed in sufficient quantity into the tissues of experimental animals, Deich-

mann and his associates (1) found that each of the compounds which they investigated (diphenyl, *o*- and *p*-aminodiphenyl, *o*- and *p*-nitrodiphenyl, and dihydroxyoctachlorodiphenyl) induced a state of intoxication, characterized by an increased respiration rate, lacrimation, loss of appetite, loss of body weight, muscular weakness, unsteadiness, and respiratory difficulties and terminated by death in coma. In addition, in some instances diphenyl caused mild paralysis of the hindlegs and mild asphyxial convulsions. All signs of illness seemed relatively mild until, without much warning, coma developed. Most rabbits and rats given lethal dosages survived for 24 to 72 hours. However, some, regardless of the compound administered, survived for only 2 hours, while others survived up to 18 days. Diphenyl is the least toxic of the group of compounds investigated. The  $LD_{50}$  dose of diphenyl and related compounds when administered orally at one time to rabbits as 25 per cent preparations in olive oil are as follows: diphenyl, 2.41 grams; *o*-nitrodiphenyl, 1.58 grams; *p*-nitrodiphenyl, 197 grams; *o*-aminodiphenyl, 1.02 grams; *p*-aminodiphenyl, 0.69 gram; and dihydroxyoctachlorodiphenyl, 0.20 gram. The repeated application upon the skin of each of these substances, except dihydroxyoctachlorodiphenyl, induced no signs of local irritation. The last named substance induced marked signs of local irritation and severe systemic poisoning. For a study of the local and systemic effects of exposure to various concentrations of the dust or vapor of diphenyl or *o*-nitrodiphenyl in air, rabbits, rats, and mice were exposed for 7 hours per day on 5 days a week over periods of time as long as 94 days. Locally, these substances in certain concentrations produced an irritation of the nasal mucosa and respiratory difficulties. Postmortem examination showed severe bronchopulmonary lesions and also minor toxic changes in the liver and kidneys. The maximum safe concentration of diphenyl in air for prolonged exposure of rabbits lies somewhere above 0.3 milligram of diphenyl per liter; for rats, it is between 0.005 and 0.04 milligram per liter; and for mice, it is somewhat below 0.005 milligram per liter of



air. The maximum safe concentration for prolonged human exposure can, according to these investigators, only be speculated upon; for the present, concentrations of diphenyl of the order of 0.005 milligram per liter should be considered dangerous. The maximum safe concentration for the prolonged exposure of rabbits to vapors of *o*-nitrodiphenyl or to dust of this compound is of the order of 0.04 milligram per liter of air. The safe concentration for prolonged exposure to vapors of *o*-nitrodiphenyl lies between 0.003 and 0.008 milligram per liter of air in the case of rats and below 0.003 milligram per liter of air in the case of mice. 4-Aminodiphenyl is at least as potent as  $\beta$ -naphthalene with reference to the production of bladder tumors, according to Walpole and his associates (2). Two years and nine months after receiving a daily dose of 2.9 to 3.3 grams per kilogram by mouth dogs were found to have advanced bladder tumors.

### Analysis

Diphenyl and *o*-nitrodiphenyl determinations in air may be carried out by a method similar to that described by Schrenk, Pearce, and Yant (3, 4). Diphenyl may be determined by means of the spectrophotometer. In a hexane solution, diphenyl shows an absorption maximum at approximately 251 millimicrons and at this point, the molecular extinction coefficient is 18,500 (5). A solution containing 0.001 per cent of the phenyl compound gives a convenient reading in a 1-milliliter cell of the spectrophotometer.

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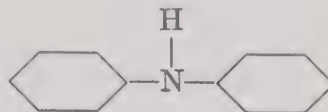
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## DIPHENYLAMINE

### Characteristics

Diphenylamine,



is a colorless crystalline solid melting at 54° C. and boiling at 302° C. (179° C. at 22 millimeters). Its density is  $d_{20/20}$  1.160. It is a somewhat pleasant smelling substance, insoluble in water, partly soluble in alcohol, and freely soluble in benzene, in ether and in carbon disulfide. It is such a weak base that its salts are completely hydrolyzed by water and therefore it is practically insoluble in dilute acids. Due to the presence of the two negative phenyl groups the hydrogen attached to nitrogen is feebly acidic and in the absence of moisture the potassium salt may be prepared. Diphenylamine is readily synthesized by a variety of methods, notably by heating chlorobenzene with 25 per cent ammonia in the presence of copper oxide or copper chloride. Diphenylamine is also formed by the elimination of water between phenol and aniline in the presence of a small amount of strong mineral acid. An important industrial process is that of heating aniline and aniline hydrochloride in a closed cast-iron vessel or autoclave for 32 hours at 200° C. The melt is then extracted with dilute hydrochloric acid and distilled under reduced pressure. Diphenylamine is extensively manufactured in this country and the export of this substance in 1952 amounted to 505,935 pounds (1).

### Uses

Diphenylamine is used in the manufacture of certain azo dyestuffs, such as orange IV and metanil yellow, and is the most reliable of all stabilizers for explosives, being

incorporated to the extent of 8 per cent with nitrocellulose powders and other high explosives (2). It is also used as an anti-aging material in rubber, as a vulcanization accelerator and as an anti-oxidant. To some extent it is used by veterinarians to combat screwworm infestation in cattle.

### Toxicity

While its toxic effects somewhat resemble those of aniline, diphenylamine is much less poisonous. Nonetheless, it is definitely toxic. Lande, Dervillee, and Collet (3) found that when diphenylamine was administered by mouth to rabbits in doses of 0.5 to 2 grams per kilogram of body weight, asthenia, wasting, and anorexia were observed over a period of 15 to 20 days, with an occasional death. Robert and his associates (4) state that poisoning in industry arises from inhalation of the vapors of alcoholic solutions of diphenylamine, partly from inhalation of the mist and dust of this compound and partly from skin contact. The clinical symptoms include bladder troubles, tachycardia, hypertension (when poisoned by the alcoholic solution), and eczema. In dust inhalation experiments over a period of 2 to 4 months animals showed definite liver, spleen, and kidney changes.

### Analysis

Owing to its many color reactions diphenylamine presents but little difficulty in detection. The blue color formed by nitric acid in the presence of sulfuric acid is well known and determination of the amount of diphenylamine dust present in the atmosphere in manufacturing operations is a relatively simple colorimetric procedure. An alternate method is that of Ponomarenko (5) in which an air sample is taken by bubbling through sulfuric acid and the diphenylamine determined colorimetrically based upon the violet-red color formed by its reaction in acid solution with diazo-sulfanilic acid.

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## ETHYL ACETATE

### Characteristics

Ethyl acetate, acetic ether, vinegar naphtha,  $\text{CH}_3\text{COOC}_2\text{H}_5$ , is a colorless, clear, volatile, inflammable liquid with a characteristic fruity odor and which when diluted has a pleasant taste. It boils at  $77.15^\circ\text{C}$ ., melts at  $-83.6^\circ\text{C}$ ., has a density  $D_{20/4}$  of 0.90055, and a refractive index of  $n_{25/D}$  1.37005. It is soluble in water to the extent of 100 milliliters per liter of water at  $25^\circ\text{C}$ . and is somewhat more soluble at lower temperatures and less soluble at higher. It is completely miscible with alcohol, acetone, chloroform, and ether. Its vapor pressure at  $20^\circ\text{C}$ . is 65 millimeters of mercury and its flash point is  $4^\circ\text{C}$ . Ethyl acetate undergoes slow hydrolysis in the presence of water acquiring an acid reaction. It forms a heterogeneous binary constant boiling mixture of boiling point  $70.4^\circ\text{C}$ . with water. Ethyl acetate is obtained by the slow distillation of a mixture of acetic acid, ethyl alcohol, and sulfuric acid. In a more recent commercial process, it is synthesized from acetylene, via acetaldehyde, the ester being obtained from the latter by the action of aluminum ethoxide. Ethyl acetate production has increased since it is a by-product of the manufacture of the vinyl acetals, which are used for safety glass for automobiles and transparent coatings for fabrics.

### Industrial Uses

The production of ethyl acetate in the United States in 1945 amounted to 105,814,000 pounds; in 1954 production was 72,451,000 pounds. This ester is widely used as a solvent for nitrocellulose, in airplane



dopes, smokeless powder, artificial leather, photographic films, artificial fruit essences, perfumes, and for the preparation of aceto-acetic ester. Ethyl acetate has been the standard medium-evaporating solvent in the lacquer industry for a number of years. While somewhat disadvantageous from the point of view of blushing and flow, it is superior to many slow-evaporating solvents with reference to viscosity. It is supplied to the lacquer industry as an 85 per cent or higher grade, the balance consisting of ethyl alcohol. Ethyl acetate is an authorized denaturant for ethyl alcohol (Specially Denatured Alcohol, Formulas 35 and 35-A).

### Toxicity

Ethyl acetate is irritating to the mucous surfaces, particularly the eyes, gums, and respiratory passages, and is mildly narcotic. On repeated or prolonged exposure, some corneal clouding has been observed. Prolonged inhalation causes acute pulmonary edema and congestion of the liver and kidneys. In chronic poisoning, secondary anemia, leucocytosis, and cloudy swelling and fatty degeneration of the viscera occurs (1). Beintker (2) has reported industrial poisoning arising from the use of ethyl acetate. Mancini and associates (3), in a pharmacological and toxicological study of methyl acetate and ethyl acetate, determined that for goldfish the lethal concentration in the water was 0.02 per cent for methyl acetate and 1.1 to 1.2 per cent for ethyl acetate. When injected subcutaneously in rats, the lethal dose was 8 grams per kilogram for methyl acetate and 5 grams per kilogram for ethyl acetate. Narcosis and death of rats was produced by inhalation of air containing 46.6 milligrams of methyl acetate per liter but not by air containing much higher concentrations of ethyl acetate. Chronic poisoning by inhalation produced pulmonary edema and cloudy swelling of the kidneys, liver, and myocardium. While Smyth and Smyth (4), in 1928, found that animals could withstand a concentration of ethyl acetate of 2000 parts per million without apparent ill effects following 65 exposures, the accepted present-day allowable concentration of ethyl acetate vapor to which workers may be exposed is lower.

### Analysis

While no specific method for the evaluation of ethyl acetate as an aerial contaminant is available, several indirect methods may be applied. The ester may be adsorbed on activated charcoal or silica gel and weighed, or it may be retained on passing air through fritted glass bubblers containing ethyl alcohol and the latter solution hydrolyzed with a known amount of standard alkali solution, followed by back-titration of the latter. It should be pointed out that ethyl acetate vapor in industry is frequently only one component of a mixture containing other esters and that either of the methods described above should be employed with this in mind. Keenan (5) has recently developed a method for the colorimetric determination of ethyl acetate which involves the conversion of the ester by hydroxylamine and the addition of ferric chloride to form a violet colored complex. Fading is not appreciable within the first few minutes.

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## ETHYL ALCOHOL

### Characteristics

Ethyl alcohol, grain alcohol, ethanol,  $C_2H_5OH$ , has a boiling point of  $78.325^\circ C.$ , a freezing point of  $-117.3^\circ C.$ , a density  $D_{20/4}$  of 0.7894, and an index of refraction  $n_{20/D}$  of 1.3610. It is a colorless, mobile liquid of pleasant odor, has a flash point of  $12^\circ C.$ , a vapor pressure at  $20^\circ C.$  of 44 millimeters of mercury, and is completely miscible with water. Ordinary commercial alcohol is a constant boiling mixture ( $78.2^\circ C.$ ) of alcohol (95.57 per cent by weight) and water (4.43 per cent).

Ethyl alcohol has been made since antiquity by the fermentation of sugar or starch in the presence of yeast. Raw materials used at industrial alcohol plants at the present time include molasses, grain (corn, malt, wheat, sorghum, rye, barley, rice, and bran), pineapple juice, whey, and cellulose pulp. It is separated from the fermented mash by distillation. Synthetic ethanol is made by hydrolysis of ethyl sulfuric acid and diethyl sulfate which is formed on absorption of ethylene in concentrated sulfuric acid. The synthetic production of alcohol from cracked petroleum gases assumed considerable importance during World War II. When oxidized with chromic acid-sulfuric acid mixture, alcohol yields acetaldehyde (boiling point 20° C.) and with alkaline permanganate, it is oxidized to acetic acid (boiling point 118° C.). When warmed with iodine dissolved in potassium iodide solution with the addition of sodium hydroxide, alcohol yields iodoform (melting point 119° C.). On slow distillation with hydriodic acid, it yields ethyl iodide (boiling point 72° C.).

### Industrial Uses

During 1945, 683,432,000 proof gallons of ethyl alcohol were produced in the United States. The allocations of ethyl alcohol for industrial purposes in 1944-45 show that approximately 51.2 per cent was used for synthetic rubber, 17.9 per cent for chemical manufacture (acetaldehyde, acetic acid, ethyl acetate, ethers, and other chemicals), 7.4 per cent for solvent uses (nitrocellulose and lacquers, shellac and resins, pharmaceuticals and cosmetics, adhesives, inks, and preservatives), 6.3 per cent for anti-freeze, 8.6 per cent for export, 4.3 per cent for explosives, and 1.5 per cent for plastics and synthetic resins.

### Toxicity

In spite of its wide application in industry, alcohol is not a serious industrial poison. In industry, the injurious effects are mainly confined to its irritant action on the eyes and upper respiratory tract. Very high concentrations of vapor may cause a slight degree of intoxication. Since ethyl alcohol is com-

pletely burned in the body to carbon dioxide and water, it is practically a noncumulative poison. The ingestion of alcohol is followed by a wide variety of symptoms, and habitual, excessive ingestion may result in damage to the brain and nervous system. Henderson and Haggard (1) state that the safe concentration for exposure to alcohol vapor during the working day ranges from 250 to 1,064 parts per million of air.

### Analysis

The concentration of ethyl alcohol vapor in air may be determined by application of one of a variety of methods which have been primarily developed for the estimation of alcohol in exhaled air. Various colorimetric methods have been proposed for the estimation of traces of ethyl alcohol, such as Schiff's reagent method and the potassium dichromate oxidation method (2, 3). The iodine pentoxide method of Haggard and Greenberg (4) is well adapted to the determination of ethyl alcohol vapor in air. In this method a measured sample is drawn into a tube containing hot iodine pentoxide. The alcohol is decomposed with the liberation of iodine which is estimated directly by titration.

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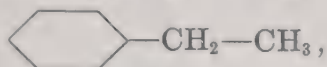
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## ETHYLBENZENE

### Characteristics

Ethylbenzene, phenylethane,



is a colorless liquid boiling at 136.187° C. and melting at -95.081° C. Its density is  $d_{20}$  0.86696 and index of refraction  $n_{20/D}$  1.49580 (1). Ethylbenzene is only slightly soluble in water, but dissolves in alcohol, benzene, carbon tetrachloride and ether. On oxidation with chromic acid, ethylbenzene yields benzoic acid and on dinitration, followed by reduction of the crude product with tin and hydrochloric acid and subsequent acetylation, ethylbenzene yields 2,4-di-(acetylamino)-1-ethylbenzene which crystallizes in small needles from methyl alcohol and has a melting point of 223° C. With picric acid, ethylbenzene forms a picrate consisting of light, yellow, crystalline plates having a melting point of 96.6° C. The Dow process for the manufacture of ethylbenzene is based on the reaction of benzene with ethylene at 87.5° C. using aluminum chloride as a catalyst.

### Industrial Uses

The production of ethylbenzene in the United States in 1945 amounted to 427,932,000 pounds; in 1954 total production was 825,010,000 pounds. Ethylbenzene is principally produced as an intermediate in the synthesis of styrene for which it is catalytically dehydrogenated at high temperatures with a yield varying of from 50 to 80 per cent. It also has very minor use in industry as a solvent and has been proposed as an anti-knock agent in airplane fuels.

### Toxicity

Ethylbenzene vapors are irritating to the eyes and the upper respiratory passages in concentrations below that which causes serious physiological response. Although ethylbenzene has narcotic properties, it does not have the deleterious effect on the blood which is observed with benzene itself. Yant, Schrenk, Waite, and Patty (2) found that

it was not possible to obtain a sufficiently high concentration in air at room temperature to kill guinea pigs in from 30 to 60 minutes. Saturated air at 20° C. contains less than 2 per cent vapor. During exposure to concentrations of 1 per cent, the symptoms observed in the order of occurrence were eye and nose irritation, apparent vertigo, static and motor ataxia, apparent unconsciousness, followed by shallow respiration, and finally slow gasping respiration followed by death after from 2 to 3 hours' exposure. Further experimental work, in which six men breathed air containing 0.1 per cent of ethylbenzene vapor, indicated that this concentration is irritating to the eyes and throat and ultimately causes dizziness.

### Analysis

The detection of ethylbenzene when present in quantity may be effected by conversion of this substance to one of its identifying compounds, such as 2,4,6-trinitro-1-ethylbenzene, *p*-ethylbenzene sulfonamide, or the picrate. Although no method of evaluation specific for ethylbenzene as an atmospheric contaminant has been devised, its determination in the absence of other organic vapors may be effected by adsorption on activated charcoal or silica gel.

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## ETHYL BROMIDE

### Characteristics

Ethyl bromide, monobromoethane, bromoethane,  $C_2H_5Br$ , is a colorless, inflam-

mable, volatile liquid of ethereal odor. It is soluble in alcohol and ether but sparingly soluble in water (1 per cent). It has a melting point of  $-115.5^{\circ}\text{C}.$ , a boiling point of  $38.4^{\circ}\text{C}.$ , density  $d_{20/4}$  1.450, a vapor pressure of 386 millimeters of mercury at  $20^{\circ}\text{C}.$ , and an index of refraction  $n_{20/D}$  1.4239. Ethyl bromide forms explosive mixtures with air under certain conditions and is also readily decomposed into volatile toxic products in the presence of flames or hot surfaces. Ethyl bromide is prepared from potassium bromide and ethyl sulfuric acid. It can also be made by the slow addition of bromine to a red phosphorus-absolute ethyl alcohol mixture after which it is distilled.

### Industrial Uses

Ethyl bromide is used as a refrigerant, as an ethylating agent in the synthesis of many organic compounds, as an extraction solvent, and as a local surface anesthetic in medicine. The manufacture of ethyl bromide in the United States amounted to 403,000 pounds in 1945. Ethyl bromide is one of the health hazards of the pharmaceutical industry (1).

### Toxicity

Waite and Yant (2) found that ethyl bromide vapors are markedly irritating to the lungs when breathed for a short period, producing an acute congestion and edema. Sayers and his associates (3) found ethyl bromide to be much less toxic than methyl bromide, the gross pathology, however, being similar. The delayed effect of exposure characteristic of methyl bromide is noted with ethyl bromide but is less evident in the latter case. Miller and Haggard (4) found that ethyl bromide is less rapidly eliminated than methyl bromide from the system and is also hydrolyzed to a lesser extent. There was no indication of an appreciable accumulation of bromide in the intracellular water. The hydrolysis appeared to occur predominately in the extracellular fluids. It is remarkable that doses as great as 800 milligrams per kilogram of ethyl bromide could be given animals intraperitoneally with no ill effects. With doses from 1,500 to 2,000 milligrams per kilogram, there

was some anesthesia but with prompt recovery; larger doses produced death. In clinical studies of workers poisoned by ethyl bromide, Reznikov (5) found that the bromine content of the blood is a useful diagnostic test.

### Analysis

While various methods have been suggested for the determination of the vapor of ethyl bromide in air, such as the flame detector or various combustion methods, it would appear preferable to base the valuation of ethyl bromide vapor upon determination of bromine itself. Ethyl bromide hydrolyzes comparatively easily in alcoholic potassium hydroxide solution yielding potassium bromide. Since fluorescein reacts readily with free bromine to form eosin and since it is possible to detect 1 part of bromine in 10 million parts of solution (6, 7), it should be possible to evaluate the ethyl bromide content of an atmospheric sample with some degree of accuracy based on some such procedure.

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## ETHYL CHLORIDE

### Characteristics

Ethyl chloride, chloroethane, hydrochloric ether or "kelene",  $\text{C}_2\text{H}_5\text{Cl}$ , is a gas at ordi-



nary temperature which, when compressed, is a colorless, highly inflammable, very volatile liquid. It boils at  $12.2^{\circ}\text{C}$ ., melts at  $-140.8^{\circ}\text{C}$ ., has a density of 0.921, and a vapor pressure of 1,000 millimeters of mercury at  $20^{\circ}\text{C}$ . Ethyl chloride is slightly soluble in water but is miscible with most of the commonly used organic solvents. It burns readily with a green, smoky flame and, because of its very low boiling point, is supplied in sealed glass containers or metal tubes. When heated with water to  $100^{\circ}\text{C}$ . in a sealed tube, ethyl chloride hydrolyzes to ethyl alcohol, a conversion which is accelerated by alkali. In diffused sunlight, chlorine acts upon it to form ethylidene chloride,  $\text{CH}_3\text{CHCl}_2$ , and other substitution products. Chlorine, in the presence of iron, converts ethyl chloride into ethylene chloride,  $\text{CH}_2\text{Cl}-\text{CH}_2\text{Cl}$ . Ethyl chloride is a by-product in the manufacture of chloral but may be prepared directly by passing hydrogen chloride into a solution of zinc chloride and ethyl alcohol. The evolved gas may be condensed to a liquid by passing it through a freezing mixture. The limits of inflammability of ethyl chloride in air, oxygen, and nitrous oxide, respectively, in pairs representing lower and upper limits are: 4.00, 14.8; 4.05, 67.2; and 2.10, 32.8 (1).

### Industrial Uses

Ethyl chloride is used as an ethylating agent but finds its chief use probably as a local anesthetic by freezing. While formerly somewhat used to produce general anesthesia by inhalation, its present use for this purpose is minor. It has had a certain amount of application for refrigeration purposes and has also had some limited use as a solvent for such substances as sulfur, phosphorus, oils, resins, and waxes.

### Toxicity

Our knowledge concerning the toxicity of ethyl chloride stems largely from its use as an inhalation anesthetic. Anesthesia is rapidly attained and disappears very promptly because of the high volatility of ethyl chloride, and it therefore has been of service as an anesthetic for minor surgery. While anesthesia is attained in from 2 to 5 minutes,

complete muscular relaxation is often absent and for general use it is often administered to induce anesthesia which is then maintained with ether. It has about the same danger as chloroform in its effect on the heart muscle. A number of fatalities have occurred in the use of ethyl chloride as an anesthetic—about one to 3,000 of those anesthetized, according to Cushny (2). There are slight symptoms of irritation following its inhalation but the toxic effect compared with other hydrogenated hydrocarbons is comparatively weak. Ethyl chloride is easily absorbed from the mucous membranes of the lungs and also from the skin. Distribution, as well as elimination, is rapid. In animal experiments, some evidence of kidney irritation and accumulation of fat occurs in the kidneys, cardiac muscle, and liver. Sayers and his associates (3) carried out extensive exposure of animals to ethyl chloride and found that while concentrations of 15 to 30 per cent were rapidly fatal, no deaths occurred in animals exposed for as long as 270 minutes to 4 per cent by volume of ethyl chloride vapor. Two per cent by volume of the vapor caused no symptoms other than slight to moderate unsteadiness and one per cent caused no distinct objective symptoms whatever. These investigators indicate that the order of toxicity at low concentration and following long exposure was least for ethyl chloride, increasing with ethyl bromide, greater with methyl chloride, and finally methyl bromide which was the most toxic of all four substances.

### Analysis

Owing to its ease of hydrolysis, ethyl chloride may be determined as an atmospheric contaminant by trapping the vapor in alkaline alcohol, followed by complete hydrolysis and determination of the resulting inorganic chloride. Combustion methods may also be used either by drawing air samples over platinized asbestos or in sufficiently high concentrations of ethyl chloride vapor by the use of a gas explosion pipette with oxygen and electrolytic gas.

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## ETHYLENE CHLOROHYDRIN

### Characteristics

Ethylene chlorohydrin, chloroethyl alcohol, 2-chloro-ethanol, 1-hydroxy-2-chloroethane,  $\text{CH}_2\text{Cl}-\text{CH}_2\text{OH}$ , is a colorless, mobile liquid with an indefinite odor somewhat resembling a mixture of ethyl alcohol and ether. It has a molecular weight of 80.49, boiling point of 128 to 132° C., melting point of -69° C., and density  $d_{20/20}$  of 1.2045, and it is miscible with water, ether, or alcohol. Its vapor tension at 20° C. is 5.8 millimeters of mercury and its flash point is 60° C. It is prepared by the action of hypochlorous acid on ethylene. The latter is obtained in large amounts from petroleum cracked in the vapor phase or from cracked natural gas. A certain amount is found in coke oven gas. The ethylene is trapped in acetone, in which it is soluble, by passing the gas through absorption towers under pressure. When this solution is sent through an expansion chamber, pure ethylene gas escapes. In practice sodium hypochlorite is used for the preparation of ethylene chlorohydrin and free hypochlorous acid is liberated only at the time of reaction with ethylene gas. When heated with water at 100° C., ethylene chlorohydrin yields glycol and acetaldehyde. With potassium hydroxide, ethylene is evolved while chromic oxide oxidizes ethylene chlorohydrin to chloroacetic acid.

### Industrial Uses

The greater part of the ethylene chlorohydrin produced is used as an intermediate for the production of such substances as ethylene glycol, amines, carbitols, indigo, malonic acid, novocaine, and, in general, for the introduction of the hydroxyethyl group in organic syntheses. It is used for treating potatoes, particularly sweet potatoes, before

planting in order to activate sprouting (1). Ethylene chlorohydrin is used as an industrial solvent especially for cellulose acetate and other cellulose esters and in the manufacture of certain insecticides.

### Toxicity

Ethylene chlorohydrin has an irritant effect on mucous surfaces and is a powerful renal, nerve, hepatic, and vascular poison. The vapor appears to be more lethal than ethylene dichloride (2). The symptoms of poisoning in man are nausea, vomiting, pains in the head and vicinity of the breast, and stupefaction. In fatal cases, lung edema with great extravasation of blood into the alveoli occurs with slight congestion of the cerebral cortex and marked edema of the cerebral hemispheres. In industry, the inhalation of ethylene chlorohydrin vapor constitutes the main hazard, but in certain operations repeated contamination of the clothes with the liquid and consequent direct skin contact occurs when proper precautions are not taken. The toxicity from skin contact has been reported as quantitatively greater than that by mouth (3). The fatal case described by Middleton (4) appears to have been chiefly caused by skin absorption. Goldblatt has revealed evidence that ethylene chlorohydrin is a cumulative poison. A number of cases of poisoning developed in a plant where the atmospheric concentration was about 18 parts per million (2). Dierker and Brown (5) reported a fatal case of ethylene chlorohydrin poisoning due to inhalation of 1 milligram per litre of air. In the seven cases reported by Koelsch (6), two of which were fatal, the atmospheric concentration of ethylene chlorohydrin does not appear to have been determined with any certainty. Goldblatt (2) recommends an atmospheric content of no more than 2 parts per million in workrooms but admits that this may be difficult to attain. The majority of the states in the United States regard the maximum allowable concentration of ethylene chlorohydrin as 10 parts per million. However, Ambrose (7) has found that ethylene chlorohydrin at a concentration of 7.5 parts per million is fatal to rats breathing it for 1 hour. Ballotta, Bertagni, and Troisi (8) de-



scribe a fatal case of poisoning caused by the ingestion of a small quantity of ethylene chlorohydrin. The symptoms of poisoning were nausea, headache, delirium, coma, and collapse.

### Analysis

In common with the other commercial chlorinated hydrocarbons, there is no specific analytical method for the evaluation of ethylene chlorohydrin as an aerial contaminant. However, it yields the reactions common to chlorinated hydrocarbons in general and in the absence of similar halogenated compounds, ethylene chlorohydrin may be quantitatively evaluated by passing the contaminated air through gas bubblers containing an absorbent with subsequent hydrolysis of the trapped ethylene chlorohydrin by an alkali. Determination of the resulting inorganic chlorides by means of the Volhard silver titration method affords an index of the amount of ethylene chlorohydrin present in the sample. Either potassium hydroxide (9) or barium hydroxide (10) may be used to effect the hydrolysis of ethylene chlorohydrin.

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tween quantity of ethylene chlorohydrin absorbed and growth response in treatments for shortening the rest period of potato tubers. *Contribs. Boyce Thompson Inst.* 8: 121 (1936).

## ETHYLENEDIAMINE

### Characteristics

Ethylenediamine, 1,2-diaminoethane,  $\text{NH}_2\text{—CH}_2\text{.CH}_2\text{—NH}_2$ , is a clear, colorless liquid with an ammoniacal odor and strongly alkaline reaction. It boils at  $116.5^\circ\text{C}$ . and melts at  $8.5^\circ\text{C}$ . Its density is  $d_{20/20}$  0.900 and its index of refraction is  $n_{26/D}$  1.4540. It is prepared by heating ethylene dibromide, or ethylene dichloride, with ammonia. Ethylenediamine is volatile with steam, is miscible with water, forming a hydrate, and dissolves in alcohol. It is slightly soluble in ether but insoluble in benzene. The hydrate melts at  $10^\circ\text{C}$ . and boils at  $118^\circ\text{C}$ . It absorbs carbon dioxide from the air on standing.

### Uses

Ethylenediamine is used as a solvent for sulfur, casein, albumin, and shellac, as an inhibitor in anti-freeze solutions, and as a rubber latex stabilizer.

### Toxicity

Carpenter, Smyth, and Shaffer (1), in their investigation of the acute inhalation toxicity of ethylenediamine, found this substance to be from 1/40 to 1/100 as toxic as ethyleneimine in single 8-hour inhalation exposures. Dernehl (2) has described 14 cases of dermatitis, three of burns, one of chronic recurrent headache, and three of asthma among workers exposed to alkyl amines, including ethylenediamine. The latter appears to be both irritating and allergenic. Sensitization occurs both on contact and inhalation with susceptible individuals. Pozzani and Carpenter (3) exposed rats repeatedly to the vapor of ethylenediamine at 484 parts per million with the result that all died within 20 days with loss of hair, kidney injuries, and somewhat less involvement of the liver and lungs. At 132 parts per million no other effect than loss of hair was appar-

ent, and no effect whatsoever was apparent at 59 parts per million. Brief human exposure to 100 parts per million was not objectionable but tingling of the skin and nose was apparent at 200 parts per million and a concentration of 400 parts per million was intolerable. Smyth (4) found that exposure of rats to 2,000 parts per million for 8 hours did not kill the animals, but 4,000 parts per million proved fatal. Death was chiefly due to kidney injury, with some injury also to the lung. The liquid ethylenediamine irritated the skin and severely injured the cornea. Smyth considers the most important effects of inhalation exposure to ethylenediamine to be respiratory tract irritation, kidney damage, and sensitization.

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## ETHYLENE GLYCOL

### Characteristics

Ethylene glycol, glycol alcohol, glycol,  $\text{HO}-\text{CH}_2-\text{CH}_2-\text{OH}$ , is a clear, colorless, syrupy liquid with a sweet taste and hygroscopic properties. It is somewhat less viscous than glycerol. Its boiling point is  $197.85^\circ\text{C}$ ., melting point  $-12.6^\circ\text{C}$ ., density  $D_{20/4}$  1.11361, and index refraction  $n_{20/D}$  1.43192. When heated with powdered potassium acid sulfate, ethylene glycol yields acetaldehyde which differentiates it from glycerol. Ethylene glycol may be obtained from ethylene bromide by heating it with sodium formate in the presence of methyl alcohol. Commercially, however, ethylene glycol is made by heating ethylene chlorhydrin with sodium bicarbonate or by heating ethylene chloride with an alkali carbonate and alcohol under

pressure. While freely soluble in water, ethylene glycol is immiscible with ether, benzene, chloroform, and a number of other organic solvents. Its vapor pressure is low and amounts to only 0.09 millimeter of mercury at  $20^\circ\text{C}$ . The vapor pressure of triethylene glycol is 0.001 millimeter of mercury at  $25^\circ\text{C}$ .

### Industrial Uses

During 1954, 637,901,000 pounds of ethylene glycol were produced in the United States. It is used as an anti-freeze for automobiles and for motor cooling and is a valuable starting material for the manufacture of explosives. Its hygroscopic and solvent properties make it useful as a softener in lacquers, printing inks, wood stains, glue mixtures, textile processing, and for moistening tobacco. It is a solvent for fruit flavors, food preparations, toilet preparations, electrical insulation compositions, and dopes. Both triethylene glycol and propylene glycol have been recommended as aerial disinfectants.

### Toxicity

Owing to its low volatility ethylene glycol is not hazardous from the point of view of exposure to its vapor at room temperature. However, it is toxic when administered by mouth and was considered by Hunt (1) to be as toxic as methyl alcohol, although less dangerous because it is not absorbed so readily. The relative acute toxicities (substances administered by stomach tube in single doses) of some glycols and derivatives were determined for mice, rats, and guinea pigs by Laug and his associates (2) and in the order of increasing toxicities are as follows: propylene glycol, diethylene glycol, ethylene glycol, diethylene glycol mono-ethyl-ether, dioxan, and ethylene glycol mono-ethyl-ether. These authors concluded as a result of both acute and chronic studies that with the exception of propylene glycol these substances should be entirely omitted from food and drug preparations. Propylene glycol should be avoided except in very small concentrations. Several deaths have been reported from drinking ethylene glycol anti-freeze fluid. The symptoms which occur are



vomiting, somnolence, prostration, stupor, and coma. Ethylene glycol taken by mouth is apparently rapidly oxidized to oxalic acid. Crystals of the latter are deposited in abundance in the renal tubules. Death may result from renal failure or acute cardiac failure. Apart from its toxicity by mouth, ethylene glycol is an unlikely industrial hazard. This also applies to numerous related glycols. Smyth and his associates (3) found the skin irritant properties of the polyethylene glycols to be negligible. Diethylene glycol used in a commercial "elixir" was the cause of mass poisoning a few years ago in which at least 73 persons died. Karel and his associates (4) found the relative toxicity of the various glycols as determined by intraperitoneal injection in mice and expressed in LD<sub>50</sub> (millimoles per kilogram) to be as follows: ethylene glycol, 90.55; diethylene glycol, 91.67; triethylene glycol, 54.27; propylene glycol, 127.87, and dipropylene glycol, 33.54. No maximum allowable concentration value for ethylene glycol has so far been established.

According to Fitzhugh and Nelson (5) triethylene glycol is less toxic to animals than diethylene glycol. The oral LD<sub>50</sub> doses of 14.8, 7.7, 23.7, and 4.4 milliliters per kilogram for diethylene glycol in rats, guinea pigs, mice, and rabbits, respectively, compare to similar doses of 16.8, 7.9, 18.7, and 8.4 milliliters per kilogram for triethylene glycol. Diethylene glycol at concentrations of 1, 2, and 4 per cent in the diet of rats for 2 years produced the toxic effects of bladder tumors and bladder stones. The extent of the lesions was related to the dosage of the glycol. Similar doses of triethylene glycol produced no toxic effect. Lauter and Vrla (6) found that rats could tolerate without toxic effect 3 per cent aqueous solutions of triethylene glycol as drinking water for 30 days, but that when 5 per cent triethylene glycol was used, the rats showed definite effects of a deleterious nature.

In investigating the use of glycol vapors for disinfecting air, Bigg, Jennings, and Fried (7) found that the concentration of propylene glycol and triethylene glycol vapors necessary to produce bactericidal action is 0.1 milligram per liter and 0.005 milligram

per liter, respectively, and that these concentrations appear to be free from health hazards and offer no fire or explosive hazard. The occupants of the treated rooms experienced no discomfort due to the glycol fumes. Triethylene glycol is preferred over propylene glycol because smaller amounts of the former are bactericidal. However, a January 1947 press release by the Director of the National Institutes of Health stated that the consensus of committees of the National Research Council and the American Public Health Association was that the use of either glycol vapors or ultraviolet radiation in reducing upper respiratory diseases is still purely in the experimental stage (8).

### Analysis

Owing to its low vapor pressure ethylene glycol is unlikely to be an aerial contaminant except as mist. Methods for the determination of ethylene glycol have been developed by Seikel (9). These depend upon either conversion to its ditrityl ether or oxidation with lead tetraacetate. Ethylene glycol may be identified by conversion to its dibromide, boiling point 129° C.; diacetate, boiling point 187° C.; dibenzoate, melting point 73° C., or dicarbanilate, melting point 157° C.

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## ETHYLENE GLYCOL MONO-*n*-BUTYL ETHER

### Characteristics

Ethylene glycol mono-*n*-butyl ether,  $\beta$ -*n*-butoxyethanol, *n*-butyl  $\beta$ -hydroxy ethyl ether or butyl "cellosolve",  $C_4H_9OCH_2CH_2 \cdot OH$ , is a colorless, mobile, odorless, or mildly rancid smelling liquid boiling at 170 to 176° C. and having a density of  $D_{15/15}$  0.9188, an index of refraction  $n_{26/D}$  1.4177, and a flash point of 74° C. Its solubility in water is 5 per cent at 20° C. The vapor pressure of butyl cellosolve is 2 millimeters of mercury at 30° C. Butyl cellosolve with phosphorus trichloride in pyridine reacts to form *n*-butyl  $\beta$ -chloroethyl ether which has a boiling point of 154.5° C.; with phosphorus tribromide in pyridine, it yields *n*-butyl  $\beta$ -bromethyl ether (boiling point 172° C.)

### Industrial Uses

Butyl cellosolve is used in industry as a solvent for cellulose nitrate and other cellulose esters and ethers. It has other solvent uses with reference to resins, oils, greases, and albumin and has occasional use in dry cleaning as a component of dry-cleaning soaps. It is also used to some extent in the paint and lacquer industry. Its principal advantage in lacquers results from its high boiling point and its delay in hardening which imparts a slight increase in gloss to the film. It, however, contributes little if anything to the flow or blushing characteristics of lacquers.

### Toxicity

Butyl cellosolve has been found to have a local irritating effect on mucous membranes and to produce kidney poisoning. The fatal dose following subcutaneous injection into mice has been found to be 0.5 milliliter per kilogram of body weight (1). Smyth and his associates (2) have determined the single dose toxicity by oral administration of butyl cellosolve for rats and guinea pigs. The  $LD_{50}$  for rats was 1.48 gram per kilogram of body weight and for guinea pigs was 1.20 gram per kilogram of body weight. Von Oettingen and his associates (3) studied the effect of exposure of mice to the vapors of butyl cellosolve at various concentrations and over various periods of time. Single 7-hour exposures of mice produce occasional lung or kidney changes. The usual sign of toxic action is dyspnea and an additional common sign at high concentrations is severe hemoglobinuria. Dogs exposed to 400 parts per million of the butyl derivative show blood changes somewhat similar to those produced by exposure to 800 parts per million of the ethyl derivative. Furthermore, the inhalation of butyl cellosolve vapor produces a moderate blood urea retention in dogs (4). Lehmann and Flury (5), in a study of chronic poisoning with various animals following repeated inhalation of 2.5 milligrams per liter of butyl cellosolve in air for 8 hours daily, found definite symptoms of kidney inflammation. With the exception of one case of a factory worker showing hematuria following exposure to butyl cellosolve vapor used as an enamel solvent (6), no other cases of poisoning have been reported in industry.

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## ETHYLENE GLYCOL MONOETHYL ETHER

### Characteristics

Ethylene glycol monoethyl ether, Cello-solve,  $C_2H_5-O-CH_2-CH_2OH$ , is a colorless liquid having a density  $D_{20/4}$  0.9297, a boiling point of  $134.8^\circ C.$ , and an index of refraction  $n_{20/D}$  1.40797. Its flash point is  $56.6^\circ C.$  and its vapor pressure at  $20^\circ C.$  is 6.2 millimeters of mercury. It is miscible with water and various organic solvents. On boiling with 48 per cent hydrobromic acid, it yields ethylene bromide (boiling point  $129^\circ C.$ ) and ethyl bromide boiling at  $158^\circ C.$  On oxidation with potassium chromate and sulfuric acid or on dehydrogenation over copper at about  $425^\circ C.$ , it yields ethoxy-acetaldehyde. The acetate is not recommended as a derivative for the identification of ethylene glycol monoethyl ether. Cello-solve is synthesized industrially by the interaction of ethylene glycol and dimethyl sulfate in the presence of sodium hydroxide. It is also prepared when ethylene oxide under pressure is pumped into an autoclave in which absolute ethyl alcohol is present in an amount slightly in excess of that demanded by theory. About a 70 per cent yield is obtained by this process.

### Industrial Uses

Since the first important solvent for nitro-cellulose was a mixture of ether and alcohol, it was felt that a single derivative consisting of a combination of the ether and alcohol groups in a single molecule would have good solvent properties for this substance. Ethylene glycol monoethyl ether, one of the first compounds of this type, was marketed under the name Cello-solve and has since been an important commercial solvent for nitrocellulose. Many similar derivatives have since

come into commercial production. Cello-solve can be diluted with nonsolvents far better than other solvents of a similar boiling range. In addition to the above use, it is used as a solvent for natural and synthetic resins, as a lacquer, and as a varnish remover.

### Toxicity

Unless inhaled in considerable amount, the toxic effects of ethylene glycol monoethyl ether are negligible. It has a slight irritating effect on the mucous membranes and in quantity produces some hyperemia of the kidneys and occasional hemorrhage into the gastric mucosa. While it has but little odor in low concentrations, in high concentrations it is found to possess a disagreeable odor which acts as a warning agent. Waite, Patty, and Yant (1) exposed guinea pigs to concentrations of the vapor of this substance in air up to that quantity which produced death. Exposure to 0.6 per cent for 24 hours caused death at the end of the exposure; exposure to 0.3 per cent for 24 hours caused death 24 hours following exposure; exposure to 0.6 per cent for 1 hour, 0.3 for 4 hours, and 0.5 for 14 hours caused no apparent harm. The minimum lethal concentration value for ethylene glycol monoethyl ether in mice was found by Werner and his associates (2) to be 6.7 milligrams per liter or 1,820 parts per million. According to Browning (3), examination of workers using lacquer-containing Cello-solve has revealed no definite symptoms and very slight physical signs which might point to changes in the liver or kidneys. Workmen who had worked with the solvent for as long as 13 years in lacquer and paint manufacture gave no indication of injury to health from this source. The maximum allowable concentration value has been set by various agencies as between 100 and 500 parts per million.

### Analysis

The determination of small amounts of ethylene glycol monoethyl ether as an atmospheric contaminant presents a number of difficulties—notably the effective trapping of the contaminant and a suitable method for its final evaluation. Werner and Mitchell (4) have devised a method which,

tested over the range of 1.36 to 10.30 milligrams per liter, is accurate within about  $\pm 4$  per cent. In this method, samples of air were secured in evacuated flasks, the organic material oxidized with known amounts of standardized potassium dichromate solution, and the dichromate consumed determined by titration. The exact conditions necessary for oxidation were carefully investigated.

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### ETHYLENE GLYCOL MONOETHYL ETHER ACETATE

#### Characteristics

Ethylene glycol monoethyl ether acetate,  $\text{CH}_3\text{COOCH}_2\text{CH}_2\text{OC}_2\text{H}_5$ , having the trade name Cellosolve acetate, is a colorless liquid with a mild, pleasant, ester-like odor. It has a boiling point of  $156.2^\circ\text{C}$ ., density  $d_{20/20}$  0.975, index of refraction at  $25^\circ\text{C}$ . 1.4030, vapor pressure 1.09 millimeters of mercury at  $20^\circ\text{C}$ . and 3.5 millimeters at  $30^\circ\text{C}$ ., and the flash point is  $65^\circ\text{C}$ . Its solubility in water is only 29 milliliters per 100 milliliters of water at  $20^\circ\text{C}$ ., but it is miscible with aromatic hydrocarbons.

#### Industrial Uses

Cellosolve acetate is a solvent for nitrocellulose, oils, and resins. As it is a high boiling solvent, it is seldom used in standard lacquers since it delays the complete hardening of the film, but it is used in some specialty lacquers to increase the gloss. For this reason, it is especially useful in automobile lacquers where it is used to retard evaporation and to impart high gloss.

#### Toxicity

The toxicity of Cellosolve acetate in mice by cutaneous injection as compared with other ethylene glycol derivatives was found by von Oettingen and Jirouch (1) to be in the following order—butyl cellosolve (most toxic), ethylene glycol, diethylene glycol, Cellosolve, carbitol, Cellosolve acetate, and dioxane. The minimum lethal dose for mice for Cellosolve acetate was 5 milliliters per kilogram of body weight. Lehmann (2) found the inhalation of 0.045 per cent of the vapor in air for 8 hours daily repeated 12 times was tolerated by two mice, two guinea pigs, and one rabbit, while one rabbit and two cats died. Smyth and his associates (3), in determining the single dose toxicity of some glycols and derivatives, found the  $\text{LD}_{50}$  of Cellosolve acetate for rats to be 5.1 grams per kilogram and for guinea pigs, 1.91 gram, which is about midway in the group of some 60 glycols and related compounds. In animal experiments, 300 to 400 parts per million show small but measurable effects on the cellular elements of the blood. The vapors may lead to eye irritation and may influence taste and odor perception. In higher concentrations, it is a central nerve depressant and may act adversely on the renal system. Though there is not much direct information on toxicity to man, the deviation from the usual blood picture may constitute a prime warning of damage (4).

#### Analysis

Seikel and Huntress (5) have devised a simplified procedure for the identification of various glycols based upon the preparation of their trityl ethers. Detailed methods of procedure and physical constants (melting point, solubility, and crystal form) are given for various Cellosolves. Quantitative determination of Cellosolve acetate as an aerial contaminant can be made by a modification of Elkins' method (6) for methyl Cellosolve.

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## ETHYLENE GLYCOL MONOMETHYL ETHER

### Characteristics

Ethylene glycol monomethyl ether, methyl Cellosolve,  $\text{CH}_3\text{OCH}_2\text{CH}_2\text{OH}$ , is a volatile liquid of not unpleasant odor with a density  $d_{20/4}$  0.9647, boiling point  $124.5^\circ\text{C}$ ., and index refraction  $n_{20/D}$  1.40238. The vapor pressure is 7 millimeters of mercury at  $20^\circ\text{C}$ . and the flash point is  $46^\circ\text{C}$ . It is completely soluble in water. Methyl Cellosolve has the most rapid rate of evaporation and the lowest boiling point of the commercially available glycol ethers. On oxidation with sodium dichromate and sulfuric acid or by dehydrogenation over copper at about  $425^\circ\text{C}$ ., ethylene glycol monomethyl ether yields methoxyacetaldehyde (boiling point  $92.3^\circ\text{C}$ .). Methyl Cellosolve is prepared by the alcoholysis of ethylene oxide with methyl alcohol.

### Industrial Uses

Ethylene glycol monomethyl ether is a solvent for cellulose esters. Its high solvent power and lack of odor make it useful as a solvent in lacquer and thinner mixtures, as well as in quick-drying varnishes and enamels. In the plastics industry, it is used in making cellulose acetate compositions. Methyl Cellosolve is one of the few solvents for cellulose acetate which boil between  $110^\circ$  and  $130^\circ\text{C}$ . and which are not too fast from the standpoint of flow and not too slow for good speed of hardening. It has the disadvantage of blushing and is therefore not suitable with nitrocellulose lacquers. In one application (the making of fused collars) the collar with a lining of cellulose acetate is treated with a solvent containing about 33

per cent methyl Cellosolve. When heat and pressure are applied, the collar becomes stiff without the use of starch (1).

### Toxicity

Starrek (2), upon exposing animals to an almost saturated (0.93 per cent) gas-air mixture of ethylene glycol methyl ether, found that a 1- to 3-hour inhalation caused a slight secretion of tears, some coordination disturbances, and, in some cases, kidney irritation in guinea pigs, cats, and rabbits. Cats and rabbits recovered, while several guinea pigs died. He found that the inhalation of 0.32 volume per cent caused equilibrium disturbances after 5 hours and prostration after about 6 hours. Werner and associates (3) found that when dogs were exposed to approximately 500 parts per million of methyl Cellosolve the most significant changes were in the blood and consisted of decreased hemoglobin and erythrocytes and increased granulocytes and reticulocytes. Approximately 800 parts per million of Cellosolve and 400 parts per million of butyl Cellosolve produced similar but less marked effects on the blood. With mice as subjects, these investigators determined the minimum lethal concentration to be 4.6 milligrams per liter or 1480 parts per million, making it second only to butyl ether in toxicity. A case of fatal poisoning due to the ingestion of methyl Cellosolve has been reported by Young and Woolner (4). Findings at autopsy in this case were mainly a hemorrhagic gastritis and toxic changes in kidneys and liver. Donley (5) reports a case of toxic encephalopathy and Parsons and Parsons (6) report two cases of toxic encephalopathy following exposure to ethylene glycol monomethyl ether. Ethylene glycol monomethyl ether has been suspected as the cause of illness among "fused collar" manufacture employees. An investigation made by Greenburg and associates (1) found the blood picture of employees as a whole to be suggestive of macrocytic anemia associated with a reduction in the platelets and an increase of young granulocytes. All of the 19 employees examined had abnormal blood pictures but clinically they fell into three groups: normal, those with abnormal neuro-

logical findings but no symptoms, and those with abnormal neurological findings and with symptoms of fatigue and drowsiness. As a result of this investigation, the authors suggested that the concentration of this substance in air be kept below 25 parts per million.

### Analysis

The analysis of air for its content of methyl Cellosolve may be made by the differential oxidation method of Elkins and his associates (7). In this method, the sample is secured with two standard impingers in series containing water. The air sample should have a volume of about 30 cubic feet. The amount of standard dichromate solution consumed by the sample is then found by titration, using potassium iodide and sodium thiosulfate with starch for the end point. This method may be employed in the presence of methyl or ethyl alcohol. Acetone interferes but can be removed by aeration.

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## ETHYLENE GLYCOL MONOMETHYL ETHER ACETATE

### Characteristics

Ethylene glycol monomethyl ether acetate, methyl Cellosolve acetate, methyl gly-

col acetate,  $\text{CH}_3\text{COOCH}_2\text{CH}_2\text{OCH}_3$ , is a stable, colorless liquid with a pleasant characteristic ester odor. It has a boiling point of  $144.5^\circ\text{C}$ ., a melting point of  $-65.1^\circ\text{C}$ ., a density  $D_{20/20}$  of 1.0067, a vapor pressure of 3.73 millimeters of mercury at  $20^\circ\text{C}$ ., a refractive index  $n_{20/D}$  1.4019, and a flash point of  $60^\circ\text{C}$ . It is miscible with water and the common organic solvents.

### Industrial Uses

Methyl glycol acetate is a solvent for nitrocellulose, cellulose acetate, other cellulose esters and ethers, and for various gums, resins, waxes, and oils. It is used in the manufacture of photographic film, lacquers, dopes, and in textile printing.

### Toxicity

Smyth and his associates (1) investigated the toxicity of ethylene glycol monomethyl ether acetate and determined the dosage-mortality curve for the substance both with rats and guinea pigs. These data were based on single doses administered by stomach tube. This investigation indicated that the esters of glycol ethers in general are less acutely toxic than the corresponding glycol ethers. The  $\text{LD}_{50}$  dose for rats was found to be 3.93 grams of the ester per kilogram of animal weight and for guinea pigs, 1.25 gram per kilogram of animal weight. In contrast with these data, the  $\text{LD}_{50}$  dose for ethylene glycol monomethyl ether itself was found to be 2.46 grams per kilogram for rats and 0.95 gram per kilogram for guinea pigs. According to Lehmann and Flury (2), no irritation followed even with repeated brushing of the undiluted substance on the skin of rabbits and inhalation of the approximately saturated vapor concentration at  $23^\circ\text{C}$ . caused only slight irritation of the mucous membrane. However, chronic inhalation experiments when carried out daily for 8 hours where the total concentration was 5 milligrams per liter caused the death of cats after 4 days and rabbits after 6 days. Guinea pigs and mice recovered, however, after such exposure. Kidney injury was found in all cases. No cases of industrial poisoning have been reported to date.



## Analysis

Several methods have been proposed for the determination of concentrations of the ethers of ethylene glycol in air as contaminants. The chemical method (3, 4) depends upon the chromic acid oxidation of the ether and titration of the excess dichromate. A physical method (5) is based upon infrared absorption spectroscopy. Morgan (6) has recently proposed a modified alkoxyl method applicable to the semi-micro quantitative estimation of ethylene glycol esters.

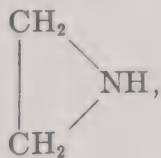
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## ETHYLENE IMINE

### Characteristics

Ethylene imine, vinylamine, ethenylamine, dimethylene imine,



the nitrogen analogue of ethylene oxide, is a colorless liquid boiling at 56° C., freezing at -71.5° C., and having a density of  $d_{20/4}$  0.8321. The vapor pressure of ethylene imine at 20° C. is 160 millimeters of mercury and its saturation concentration at that temperature is 376 milligrams per liter (214,000 parts per million) (1). Ethylene imine is very soluble in water and in ether, but some-

what less soluble in alcohol. Liquid ethylene imine smells strongly of ammonia and has basic properties. The compound is very reactive and the ring structure is readily broken. It combines with hydrobromic acid in the cold to form bromoethylamine; with hydrogen sulfide to form thiodiethylamine; with sulfur dioxide to form taurine. With benzenesulfochloride and alkali, it forms a sulfonamide insoluble in alkali. Ethylene imine may be prepared from bromoethylamine by withdrawal of hydrogen bromide with silver oxide or caustic potash.

### Industrial Uses

Ethylene imine is chiefly of interest in organic synthesis—particularly as an intermediate in the production of compounds of importance in the textile industry.

### Toxicity

While ethylene imine has for some time been known to have a corrosive effect on skin contact, systemic poisoning arising from exposure to the vapor of this substance has been a matter of only comparatively recent investigation. Danehy and Pflaum (2) reported in 1938 that there was no discomfort during exposure to ethylene imine, but that after 2 hours there was nausea and vomiting with inflammation and swelling of the epithelium of the mouth, throat, and eyes. The symptoms disappear within 1 or 2 days. These investigators also found that 2 drops of the liquid dissolved in 0.5 milliliter of water and injected into the shoulder of a cat caused paralysis of the hind quarters within 1 hour and death in 10 hours. Silver and McGrath (1) found that on exposure of mice to ethylene imine, the only observable symptom was irritation of the eyes and nose 1 or 2 minutes after insertion into the chamber and throughout the exposure. On removal from the chamber, the mice quickly presented a normal appearance. Deaths, preceded by extreme prostration and complete lack of muscular coordination, began to occur about 24 hours after exposure and continued over the 10-day observation period. The LD<sub>50</sub> of ethylene imine for mice, for an exposure period of 10 minutes and an observation period of 10 days, was 3.93 milligrams per liter (2,236 parts per million).

The LD<sub>50</sub> of ammonia for mice under the same conditions was found to be 7.06 milligrams per liter (10,152 parts per million). Despite the fact that both compounds are strongly alkaline, Silver and McGrath conclude that the modes of physiological action are different. Smyth and his associates (3) found a similar delayed death in the case of guinea pigs and rats. The inhalation of ethylene imine vapors at concentrations of 25 parts per million and above for 8 hours killed rats and guinea pigs by a combination of lung injury and necrosis of the kidney tubular epithelium. Death may be delayed several days after an asymptomatic period. In single exposures, it was found to be several times as toxic as some commonly used amines. In addition to its systemic effect, the fluid penetrates the skin (although the vapors do not) and it is a skin sensitizer and necrotizing agent.

### Analysis

Owing to its basic properties, ethylene imine vapor may be determined by neutralization with a standard solution of acid. A known volume of air containing this contaminant may be drawn through fritted glass bubblers containing a measured amount of nonvolatile standard acid, such as sulfuric acid, and the excess of acid back-titrated with standard alkali.

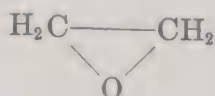
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## ETHYLENE OXIDE

### Characteristics

Ethylene oxide,



is a combustible gas at ordinary temperatures and a mobile, colorless liquid below 12° C. Ethylene oxide has a boiling point of 10.7° C., a melting point of -111.7° C., a density  $D_{0/4}$  of 0.89713, and a refractive index  $n_{D/20}$  of 1.3597. Its vapor pressure at -20° C. is 1.09 millimeters of mercury. It is miscible with water in all proportions and soluble in alcohol, ether, and other organic solvents. When ethylene oxide in aqueous solution is allowed to stand in contact with a small amount of zinc chloride or potassium hydroxide, it yields a polymeric crystalline form which melts at 56° C. When passed into cold hydrobromic acid, it yields ethylene bromohydrin. Ethylene oxide, which was first prepared by Wurtz in 1859, is made by the action of caustic alkali on ethylene chlorohydrin.

### Industrial Uses

Ethylene oxide is used as a fumigant for foodstuffs and textiles since its vapor is highly toxic to insects and their eggs. This use which was first proposed by Cotton and Roark (1) in 1928 has the advantage over certain other fumigants in that its toxicity to man is not very great and its low boiling point permits its use at relatively low temperatures. It is also marketed for this purpose under the trademark Carboxide, which is a mixture of 90 per cent carbon dioxide and 10 per cent ethylene oxide. The addition of the carbon dioxide reduces the flammability of the ethylene oxide so that there is no fire hazard and this mixture has wide application as a fumigant in warehouses and mills. Two pounds of ethylene oxide per thousand cubic feet of space is sufficient for effective fumigation of foodstuffs and textiles. In its use against the yeasts, molds, and bacteria that attack food, 1 milliliter of a 20 per cent ethylene oxide solution per liter of air at 86° F. for 3 hours is necessary for complete killing (2).

### Toxicity

Exposure to ethylene oxide produces eye and nasal irritation, blood-tinged serous exudate in the nostrils, unsteadiness, inability to stand, respiratory disturbance, dyspnea, and death, according to Waite and his as-



sociates (3). The principal pathological change noted in animals exposed to this gas is marked irritation of the respiratory system. Exposure to 5 to 10 per cent of ethylene oxide causes death in a few minutes. Three-tenths per cent is the maximum for 60 minutes without serious disturbances and 0.025 per cent is the maximum allowable concentration for several hours without serious disturbances. Ethylene oxide, according to these investigators, is less harmful than hydrogen chloride and sulfur dioxide, but is more harmful than chloroform and carbon tetrachloride. In high concentrations, the irritant properties of ethylene oxide are useful as warning of danger. When rubber gloves are worn in working with ethylene oxide the rubber absorbs the ethylene oxide to a marked extent causing dermatitis, according to Royce and Moore (4). While ethylene oxide has been suggested as a sterilizing agent for food products, Hawk and Mickelsen (5) warn against such use. In animal experiments they found that, when the foodstuff was treated with ethylene oxide, its nutritional properties were impaired.

### Analysis

The concentration of ethylene oxide vapor in air may be determined, according to Waite and his associates (3), by absorption of the oxide in water, in which it is readily soluble and to which a measured amount of 2 normal concentrations of hydrochloric acid has been added. The ethylene oxide and hydrochloric acid react to form ethylene chlorohydrin. The excess acid is titrated with standardized barium hydroxide solution, as sodium or potassium hydroxide are unsatisfactory for this purpose. In comparison with adsorption on activated charcoal, good agreement was found by this method. Hollingsworth and Waling (6) have recently modified Lubatti's method (7) in which air containing ethylene oxide is bubbled through a dilute sulfuric acid solution containing a high concentration of magnesium bromide. The excess or unconsumed acid is found by titration.

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## ETHYLENE TETRAFLUORIDE

### Characteristics

The importance of fluorinated hydrocarbons has increased enormously within the past few years as new compounds have been prepared and as the unique properties of these substances have been discovered. Anhydrous hydrofluoric acid has been firmly established as an alkylation catalyst in the petroleum industry; the chlorofluorohydrocarbons are widely used as refrigerants, and dichlorodifluoromethane serves as an excellent propellant in insecticide bombs. Ethylene tetrafluoride monomer is a colorless, odorless gas having a boiling point of  $-76.3^{\circ}\text{C}$ . and a freezing point of  $-142.5^{\circ}\text{C}$ . Several methods have been proposed over the past 60 years for the synthesis of tetrafluoroethylene, but this difficult task was accomplished in a satisfactory manner only in 1933 by Ruff and Bretschneider (1) who prepared the substance by decomposing tetrafluoromethane in the electric arc. However, tetrafluoroethylene remained of academic interest only until Plunkett (2) found that tetrafluoroethylene may be polymerized by subjecting it to superatmospheric pres-

tures in the presence of a catalyst, such as zinc chloride or silver nitrate.

### Uses

Polytetrafluoroethylene (Teflon) does not absorb water and is unaffected by prolonged contact with it. Its electrical properties are such that it is an especially valuable organic insulating product and special application has been made of seamless coated wire in which the polymer is extruded about the wire to form a plastic sheath. The chemical, electrical, and thermal stability of the tetrafluoroethylene polymer has made this substance noteworthy in the field of plastics. The present uses are varied. It has wide application in gaskets, valve stems, pipes, and tubing in the chemical industry where strong corrosive agents are in use (3). Its ability to withstand heat where other plastics are affected is exceptional and its use in electrical insulation for ultra high frequency has made it valuable for use in chemical plants where corrosive effects are unusually severe for electric wires and cables. No data are yet available regarding the output of tetrafluoroethylene in the United States nor the extent to which the polymer is manufactured.

### Toxicity

The polytetrafluoroethylene product is extremely resistant to corrosive agents and vapors. None of the common reagents, such as boiling mineral acids, aqua regia, boiling alkalis, etc., affect the product in the slightest. No substance has been found that will dissolve, or even swell, the polymer. None of the organic solvents affect it and only molten alkali metals appear to attack it. Such a substance would be expected to be physiologically inert and in fact the polymer has been rated as nontoxic (4). However, when polytetrafluoroethylene is heated above 400° C. volatile gases are evolved which have not been completely identified and the possibility exists that some of these products may be toxic. On the other hand the polymer may be heated to 300° C. for long periods of time with no change in composition and may be baked at 390° C. with only a minute loss in weight. In the mechani-

cal working of polytetrafluoroethylene dust or gases may be given off owing to frictional heat where local high temperatures may momentarily occur. According to Stokinger (5) two types of industrial exposure may possibly be harmful. Inhalation of the dust of Teflon appears to produce a condition resembling metal fume fever. This effect disappears after 24 hours with no after-effects. The second type of reaction results from inhalation of a very fine sublimate believed to contain adsorbed hydrogen fluoride. Pulmonary edema may result. Seven cases of fume fever were reported by Sherwood (6) among men working with polytetrafluoroethylene.

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## ETHYL FORMATE

### Characteristics

Ethyl formate, formic ether,  $\text{HCOOC}_2\text{H}_5$ , is a water-white, unstable liquid with a pleasant, aromatic odor. It has a boiling point of 54.2° C., a melting point of 79.4° C., density  $d_{20/4}$  of 0.92247, index of refraction  $n_{20/D}$  of 1.3597, flash point -19° C., and a vapor pressure of 200 millimeters of mercury at 20.6° C. At 20° C., 10 per cent by volume is soluble in water. It is miscible with benzene, alcohol, and ether. In contact with water, it gradually hydrolyzes into formic acid and alcohol. Ethyl formate forms no constant boiling mixture with either ethyl alcohol or formic acid. It does, however, form a binary constant boiling mixture having a boiling point of 62.8° C.



with chloroform, the mixture having the composition 13 per cent ethyl formate and 87 per cent chloroform. Ethyl formate is prepared by heating ethyl alcohol with formic acid in the presence of sulfuric acid followed by distillation.

### Industrial Uses

An estimate of the importance of ethyl formate in industry is indicated by the fact that production in the United States in 1953 amounted to 215,000 pounds. As in the case of certain other alkyl esters, ethyl formate has properties which make it suitable for use as a flavoring agent in such products as lemonades and essences. It is also used for the manufacture of artificial rum and arrac. Perhaps its principal use is in the solvent industry, since ethyl formate is a good solvent for nitrocellulose. It is used in the synthesis of organic compounds and as a fungicide and larvicide for dried fruits, tobacco, and cereals.

### Toxicity

The toxic effects of ethyl formate are primarily those of irritation and narcosis. Even after a short period of exposure, ethyl formate produces such pronounced irritation of the eyes and upper respiratory mucous surfaces that further exposure is difficult to endure. This doubtless is due to the slow hydrolysis which occurs in contact with moist surfaces with the corresponding formation of formic acid. As is well known, formic acid is extremely painful in contact with mucous surfaces and as a consequence the irritant action of ethyl formate far transcends that of ethyl acetate or ethyl butyrate. According to Flury and Zernik (1), a concentration of 330 parts per million produces slight irritation of the eyes and rapidly increasing irritation of the nose. The symptoms subside only after several hours. In air heavily contaminated with ethyl formate, deep narcosis occurs within a few minutes, followed by death within a few hours. While ethyl formate has an irritant action on mucous membranes and produces paralysis of the central nervous system, it is apparently less toxic than either butyl or amyl formate, according to Browning (2). Flury and Zernik state

that the narcotic dose is the same as the lethal dose, *i.e.*, 10,000 parts per million. No industrial poisoning with ethyl formate has so far been reported.

### Analysis

While no specific method of analysis has been developed for the determination of ethyl formate as an aerial contaminant, advantage can be taken of the ease with which this material is hydrolyzed in alkali. In the absence of other esters, air samples can be passed through alcohol, hydrolyzed with a known amount of standard solution, and back-titrated with standard acid.

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## ETHYL OXALATE

### Characteristics

Ethyl oxalate, diethyl oxalate, oxalic acid diethyl ester, diethyl ethanedioate,  $C_2H_5OOC \cdot COOC_2H_5$ , is a liquid, boiling at 185.7° C. It melts at -40.6° C. and has a density of  $d_{20/4}$  1.0785. Its index of refraction is  $n_{20/D}$  1.41011. Ethyl oxalate may be prepared directly from anhydrous oxalic acid and ethyl alcohol without a catalytic agent. The water formed during the reaction can be removed azeotropically (1). The ester has an aromatic odor, distills without decomposition, but is extremely readily hydrolyzed. It is miscible with alcohol, ether, and other organic solvents.

### Uses

Ethyl oxalate is used in the manufacture of ethyl benzyl malonate, phenobarbital, triethylamine and other compounds, dye-stuff intermediates, and plastics. It is a solvent for cellulose nitrate and acetate and is used in the perfume industry.

### Toxicity

Owing to the rather high boiling point of ethyl oxalate one would not expect it to

present a very great inhalation hazard. However, it has been used together with butyl acetate as a solvent for cellulose esters used in spray painting. Desoille and his associates (2) found that workmen exposed to concentrations varying from 0.76 milligram per liter to 0.46 milligram per liter of ethyl oxalate in air have a lowered erythrocyte count, a somewhat lower white cell count, slight eosinophilia, and sometimes neutropenia. These symptoms appeared after about four weeks of daily exposure. When rabbits were similarly exposed they developed a slight anemia.

While no fatal cases of poisoning from ethyl oxalate have been reported, it should be considered a potentially toxic substance. On inhalation hydrolytic cleavage would be anticipated, with resultant irritant action of the liberated oxalic acid (*q.v.*). Adequate ventilation should therefore be provided where the possibility of exposure to ethyl oxalate exists.

### Analysis

While no method has been reported for the analysis of air samples containing ethyl oxalate, advantage could be taken of its ease of hydrolysis. Refluxing in alkaline solution, followed by distilling off the alcohol, with subsequent acidification and permanganate titration, should prove an effective procedure. A cleaner separation would doubtless follow precipitation as calcium oxalate prior to titration.

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## ETHYL SILICATE

### Characteristics

Ethyl silicate, tetraethyl *o*-silicate,  $\text{Si}(\text{O} \cdot \text{C}_2\text{H}_5)_4$ , is a colorless, inflammable liquid of faint ethereal odor having a boiling point of 165 to 166° C., a freezing point of -77° C., a specific gravity of  $d_{20/4}$  0.933, an index of refraction of  $n_{25/D}$  1.439, and a flash point of 52° C. It is insoluble in water and

slowly hydrolyzes in contact with this medium to alcohol and silicic acid, which in turn dehydrates to an adhesive form of silica. It is miscible with ethanol. The miscibility characteristics of three component systems in which other solvents, such as acetone or ethanol and water, are used have been investigated by Cogan and Setterstrom (1). The hydrolysis of ethyl silicate is accelerated by the addition of minute amounts of mineral acids.

### Industrial Uses

Ethyl silicate is becoming increasingly important commercially as new uses are found for its singular properties. It is used as a preservative and hardening agent for stone and concrete and as a weatherproofing and waterproofing cement. Some application has been found for it as a vehicle for specialty surface coatings where heat resistance or adherence to glass is required. It is used as a bonding agent for comminuted materials. The sticky colloidal silica formed by hydrolysis dries to a hard, vitreous-like substance that is insoluble in water, will withstand high temperatures, and is inert with reference to surrounding material. It is especially valuable as a binding agent in molds for casting metals in which exacting dimensions must be maintained and where machining cannot be done. Paints formulated with ethyl silicate and containing inert pigments are resistant to heat and chemical fumes and are fire-retardant. Although nitrocellulose and other cellulose esters formulated with ethyl silicate show good adhesion to glass, even better results are obtained with hydrolyzed solutions.

### Toxicity

The physiological properties of ethyl silicate have been investigated by Kasper, McCord, and Fredrick (2) and by Smyth and Seaton (3). The former concluded that 1,060 to 2,350 parts per million is fatal to rats after 4 hours of exposure. Smyth and Seaton noted the symptoms in guinea pigs following exposures of various periods of time to concentrations varying between 395 and 3070 parts per million both in air of 70 per cent humidity and also at several concentrations in dry



air. The symptoms exhibited by the animals were in order of development: irritation of the eyes and nose, lacrimation, tremors, respiratory difficulty, and narcosis. These investigators found that exposure to approximately 2,000 parts per million is the maximum exposure for 60 minutes without the production of serious disturbances in guinea pigs and rats. The maximum exposure for several hours without causing serious disturbances is 500 parts per million. Ethyl silicate has moderate warning properties to man in concentrations uninjurious to guinea pigs and rats even after several hours of exposure. In man, 1,200 parts per million has been found to have lacrimatory properties; 700 parts per million mildly stings the eyes and nose; and 250 parts per million makes the eyes and nose tingle slightly, while 85 parts per million may be detected by its odor (3). Pozzani and Carpenter (4) on exposing rats to approximately 400 parts per million of ethyl silicate for 7 hours daily for 30 days found a significant mortality and also kidney, liver, and lung damage. However, exposure at lower concentrations resulted only in a decrease in the kidney weights of mice. On the basis of these experiments it was concluded that there seems no justification for any change in the figure of 100 parts per million that has been suggested as an hygienic standard.

### Analysis

Smyth and Seaton (3) determined ethyl silicate by adsorption on activated charcoal and frequently checked this by use of the interferometer. Parallel humidity measurements were also made. A method based upon the colorimetric determination of the blue reduced complex of silicomolybdic acid has been developed by Gurvits and Sergeeva (5).

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## FLUOROACETIC ACID

### Characteristics

Monofluoroacetic acid, fluoroacetic acid,  $\text{FCH}_2\cdot\text{COOH}$ , a crystalline substance at room temperature, melts at  $33^\circ\text{C}$ . and boils at  $165^\circ\text{C}$ . It may be obtained by the hydrolysis of its methyl ester (boiling point  $104^\circ\text{C}$ .) which in turn is prepared from methyl iodoacetate by heating with either silver fluoride, or mercurous fluoride at  $170^\circ\text{C}$ . (Swarts, 1). The acid is to a certain extent combustible, burning with a greenish flame. The C—F bond of fluoroacetic acid is very stable and the fluoroacetates do not yield the fluoride ion by hydrolysis with water alone, and even boiling with alkali splits off only a fraction of the fluoride portion of the molecule. As a consequence the determination of small amounts of fluoroacetate in biological material is fraught with difficulty. Monofluoroacetic acid is the strongest acid of the monohalogenated acetic acids. It is also by far the most toxic of the group. The  $\text{LD}_{50}$  for mice following oral administration of the sodium salt is 17 milligrams per kilogram of body weight. For comparison, that of the corresponding salt of iodoacetic acid (the next most toxic of the group, and which incidentally has the least dissociation constant of the monohalogenated acetic acids) is 63 milligrams per kilogram of body weight. Furthermore the rupture of the C—F linkage is difficult and the fluoroacetates do not exert their toxic effects by the liberation of fluorides, but instead produce these effects apparently as molecular entities.

### Toxicity

Although monofluoroacetic acid had first been synthesized more than 40 years previously, it was not until the early years of

World War II that this acid and its derivatives received any attention relating to their physiological properties. These unusual properties soon became evident in an investigation of the fluoroacetates and allied compounds, carried out by McCombie and Saunders (2) at Cambridge University in the early years of the war. It was shown that, provided the correct groupings are present, many of these substances are highly toxic (by inhalation, injection, and, to some extent, by skin absorption) and may be described as convulsant poisons with a delayed action. The original conclusion that this toxic effect is entirely due to fluoroacetic acid, which is formed either by hydrolysis or by oxidation, is now considered to be not invariably true. Chenoweth (3) has pointed out that the toxicity of compounds forming fluoroacetate *in vivo* is not due entirely to the formation of fluoroacetate. He states that  $\gamma$ -fluorobutyrate exerts a toxic action independently of any fluoroacetic acid which may be formed by the  $\beta$ -oxidation of  $\gamma$ -fluorobutyric acid. The mechanism of the toxic action of the two acids differs markedly.

Sodium fluoroacetate has been found to inhibit the spontaneous contraction of smooth muscle (4) and markedly inhibits the oxygen consumption of isolated rabbit intestinal smooth muscle in the presence of glucose (5). However, it apparently does not affect anaerobic glycolysis. Clarke and Riker (6) found that the fluoroacetate salts cause a progressive decrease in the contractility of the frog sartorius muscle.

The use of sodium fluoroacetate, also known as "1080", spread rapidly for a few years following its discovery as a powerful rodenticide; however, not all rats are equally susceptible to this poison. Kalmbach (7) found the LD<sub>50</sub> dose for the wood rat to be 5 milligrams per kilogram of body weight, 5 milligrams per kilogram for wild Norway rats, 2.5 milligrams per kilogram for tame white rats and 0.1 milligram per kilogram for wild black rats. On the other hand, Dicke and Richter (8) found the median lethal dose of sodium fluoroacetate for wild Norway rats to be 0.22 milligram per kilogram. The latter investigators compared the lethal

dose of this salt with that of "Antu" (1-(1-naphthyl)-2-thiourea) and found the median lethal dose of the latter to be 6.9 milligrams per kilogram for wild Norway rats. Hagen and his associates (9) found some evidence to indicate that the rat possesses the capacity for metabolizing sodium fluoroacetate. Distribution through the tissues is rather uniform throughout the animal poisoned with this salt. Somewhat later Peters *et al.* (10) found that the toxic effect of fluoroacetic acid in mammals is due to enzymatic conversion in the kidney to form optically active monofluorocitric acid, which competitively inhibits the metabolism of citric acid. It is of interest that Hutchens and his associates (11) found that when ethyl alcohol was subcutaneously injected in certain animals (mice, rabbits, and guinea pigs, but not dogs) the mortality following the administration of sodium fluoroacetate was significantly lowered. Scales (12) has made the interesting observation that "1080" when used as a rat poison was very deadly to dogs after eating rats poisoned in this way.

Several cases of poisoning among children have occurred as a result of accidental contact with sodium fluoroacetate. For instance, Gajdusek and Luther (13) report a case in which a 2-year-old child licked crystals from the stopper of a bottle of "1080" and became ill with symptoms closely paralleling those observed in animal experiments. The child recovered and was discharged as well on the eleventh day. Partly because of its very toxic nature, but chiefly because it has been replaced by more suitable rodenticides, the use of sodium fluoroacetate has decreased considerably.

### Analysis

While monofluoroacetic acid and its salts present certain analytical difficulties, some progress has been made in the direction of their determination. Eisenberg and Wilson (14) have found that the barium salt, Ba(FCH<sub>2</sub>.COO)<sub>2</sub>, is convenient for crystallographic identification, while Hutchens and Kass (15) have developed a colorimetric microanalytical method. The latter is based upon the fact that soluble lanthanum salts



react in the presence of acetates to form basic lanthanum acetate, which, in the presence of iodine, adsorbs the latter with the formation of a blue color.

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## THE FLUOROCARBONS

### Characteristics

While the monofluorinated hydrocarbons are markedly unstable, polyfluorides in which more than one fluorine atom is attached to the same carbon atom are distinguished by their chemical inertness. This

stabilizing effect also extends to other halogen atoms. For instance, dichlorodifluoromethane is very resistant to hydrolysis or even to molten sodium. 1,1,1-Trifluoroethane can be heated to 75 to 80° C. with fuming nitric acid without decomposition. Owing to this chemical inertness the fluorocarbons are not usable for most chemical processes or as reactants. The chlorine-containing fluorocarbons have been used for some time as refrigerants under the trade name of Freons. These are found in commerce as Freon-11 (trichloromonofluoromethane,  $\text{CCl}_3\text{F}$ ), Freon-12 (dichlorodifluoromethane,  $\text{CCl}_2\text{F}_2$ ), Freon-21 (dichloromonofluoromethane,  $\text{CHCl}_2\text{F}$ ), Freon-113 (trichlorotrifluoroethane,  $\text{C}_2\text{Cl}_3\text{F}_3$ ), and Freon-114 (dichlorotetrafluoroethane,  $\text{C}_2\text{Cl}_2\text{F}_4$ ). The fluorocarbons have nearly the same freezing and boiling points as hydrocarbons of the same structure and number of carbon atoms. They are characterized by relatively high fluidities and low surface tensions. They are completely resistant to oxidation and do not burn. These singular properties have made the fluorocarbons very important and potentially valuable. Fourteen papers of a 53-paper symposium on fluorine chemistry (American Chemical Society, 1946) deal with the industrial scale development of fluorocarbon processes (1).

### Industrial Uses

Prior to World War II the only fluorocarbons of commercial importance were the Freons, especially Freon-12 ( $\text{CCl}_2\text{F}_2$ ), which is important in refrigeration, in air conditioning, and in aerosol bombs. Rapid developments are occurring in this field moreover and the spectacular developments in the commercial generation and handling of fluorine will doubtless bring about further extensive changes. The fluorocarbon plastic, Teflon, made by the polymerization of tetrafluoroethylene, is a new commercial product of great interest because of its unique properties. It is thermally stable and chemically inert and has been very successfully applied in the commercial production of fluorine. The properties of the fluorocarbons indicate possible uses for heat transfer and as dielectric media in the manufacture of thermal

and chemical resistant plastics, and as high temperature lubricants and fire extinguishing agents (2, 3).

### Toxicity

The chemical inertness of the fluorocarbons is reflected in their physiological properties. Dichlorodifluoromethane has little if any anesthetic or toxic action. Trichloromonofluoromethane is said to have an intoxicating effect on animals in a concentration over 4 per cent in air for an exposure in excess of 1 hour, but has apparently no secondary toxic action (4). Monofluorotrichloromethane is only slightly toxic and only in such high concentrations as 10 volumes per cent or more, causes irritating symptoms, cramps, and paralysis (5). Fluoroform and 2,2-difluoropropane are so stable that they may be substituted for the nitrogen of air and guinea pigs can exist in such an atmosphere without harmful effects (6). In general, one would anticipate but very little toxic effect from inhalation of the fluorocarbons because of their thermal stability and resistance to chemical reaction. However, one must not lose sight of the fact that very high temperatures—flames and hot metals—may cause some decomposition with the formation of such irritating and toxic substances as hydrogen fluoride and hydrogen chloride.

### Analysis

The evaluation of the fluorocarbon content of air presents certain difficulties, owing to the unreactive nature of this contaminant. The most useful method of sampling probably is that of securing samples in evacuated flasks or by air displacement. Teston and McKenna (7) have recently devised a semi-micromethod for the simultaneous determination of carbon, fluorine, and chlorine in fluorocarbons. This method could possibly be used for the analysis of air samples providing the latter were sufficiently ample. The apparatus devised by Timmis for the detection and estimation of chlorinated hydrocarbon vapors in air has also been applied by that investigator to the detection and analysis of Freon in air (8).

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## FORMALDEHYDE

### Characteristics

Formaldehyde, formic aldehyde, formalin (in 40 per cent solution),  $\text{HCHO}$ , is a gas, boiling at  $-21^\circ \text{C}$ . Commercially, formaldehyde is an aqueous solution containing 37 per cent by weight, or 40 per cent by volume, of the gas. This solution usually contains 10 to 15 per cent methanol in order to prevent polymerization. An aqueous 30 per cent formaldehyde solution forms a constant boiling solution (boiling point  $98.8^\circ \text{C}$ ). The refractive indices of aqueous solutions are proportional to the concentration. Formaldehyde has a pungent and characteristic odor. With ammonia, it forms hexamethylenetetramine with evolution of heat. With Nessler's solution, it forms a reddish-brown precipitate, becoming yellowish-grey on standing. On warming with  $\beta$ -naphthol in alcohol in the presence of hydrochloric acid, it yields methylene di- $\beta$ -naphthol, a crystalline precipitate of white needles. Formaldehyde reduces Tollen's reagent and Fehling's solution. The basic process for the manufacture of formaldehyde consists of the oxidation of methanol, using either copper or silver as a catalytic agent. An iron-molybdenum oxide catalyst apparently gives a somewhat higher yield than the silver cata-



lyst, but is offset by the larger plant investment required. Petroleum gases are also used as starting material, and, apart from the plant investment, have the advantage of low operating cost.

Paraformaldehyde  $(\text{CH}_2\text{O})_n\text{H}_2\text{O}$ , a polymerization product of formaldehyde, which is also incorrectly known as "trioxymethylene", is a white, amorphous powder with a strong odor of formaldehyde. On heating or on distillation with dilute sulfuric acid, it depolymerizes to ordinary formaldehyde. It is a combustible solid with a melting point of about 120 to 130° C. and a flash point of 71° C. Paraformaldehyde is a convenient source of ordinary formaldehyde.

### Industrial Uses

In 1954, the consumption of formaldehyde in the United States was 1,032,026,000 pounds, of which more than 50 per cent entered into the production of phenolic urea, melamine, and other resins. The production of formaldehyde in the United States in 1947 was 522,440,000 pounds. Among other chemical requirements for formaldehyde are the processing of hexamethylene tetramine, pentaerythritol, ethylene glycol, paraformaldehyde, hydroxyacetic acid, and citric acid (1). The tanning industry and agriculture use notable amounts. Paper impregnated with gelatin, glue, or starch is made water-resistant with formaldehyde. Formaldehyde is also somewhat extensively used in printing and vat dyeing.

### Toxicity

Formaldehyde is a protoplasmic poison and is primarily irritant, rather than narcotic, in action. Its irritant action on all mucous surfaces is related to its chemical reactivity and the formation of irreversibly coagulated protein products. In addition to this effect, partial oxidation occurs in the tissues following absorption with the formation of formic acid. The gas is very irritant on inhalation, causing stinging and prickling in the nose and throat, salivation, tears, bronchial irritation, and catarrh. More prolonged exposure may cause anuria, soft necrotic nails, and gastroenteritis. In addition to the effect of formaldehyde gas on the eyes

and respiratory tract, irritant effects on the skin frequently follow contact with the solution in industry, or from contact with dust in the manufacture of formaldehyde resins and plastics (2). Concentrations of formaldehyde as low as 20 parts per million cause definite irritation to the eyes and upper respiratory tract.

### Analysis

Formaldehyde may be detected by its condensation with resorcinol, or with gallic acid. For instance, (a) mix 1 drop of 0.5 per cent aqueous resorcinol solution with 1 milliliter of weak formaldehyde solution and allow this to flow on to 3 to 5 milliliters of concentrated  $\text{H}_2\text{SO}_4$ . Rotate the two layers gently. In the presence of  $\text{HCHO}$ , a red ring tinged with violet will appear. Then, (b) repeat (a), using 6 drops of a cold saturated alcoholic solution of gallic acid in place of the resorcinol. A blue ring is formed in the presence of  $\text{HCHO}$ . In common with other aldehydes, formaldehyde gives a violet-blue color with Schiff's reagent.

Formaldehyde may be determined colorimetrically by its reaction with phenylhydrazine hydrochloride in the presence of potassium ferricyanide (3). When a dilute solution of formaldehyde (10 milliliters) is treated with 2 milliliters of a 1 per cent solution of phenylhydrazine hydrochloride, 2 milliliters of a 2.5 per cent solution of potassium ferricyanide, and 3 milliliters of concentrated hydrochloric acid, a violet-colored solution is obtained, which may be matched against a series of standard solutions of formaldehyde similarly treated.

Barnes and Speicher (4) utilized the colorimetric phenylhydrazinehydrochloride—potassium ferricyanide method in comparison with the dropping of mercury electrode method for determining the concentration of formaldehyde in air and found both methods suitable for this purpose. More recently, Bricker and Johnson (5) have developed a spectrophotometric method utilizing the reaction of formaldehyde with chromotropic acid to give a purple color. Formaldehyde was the only aldehyde found to give a color with this reagent. This method is described as rapid, accurate, and so sensitive that as

little as 1 microgram of formaldehyde can be detected in 1 milliliter of solution. The accuracy of the method in general is well within 5 per cent. A specific field test for formaldehyde based on this reaction has been devised by MacDonald (6). Zurlo and Griffini (7) have modified Schryver's reaction for field purposes and are able to determine atmospheric formaldehyde in the range of 0.5 to 30 micrograms with a precision of  $\pm 2$  per cent.

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### FORMIC ACID

#### Characteristics

Formic acid, formylic acid, methanoic acid,  $\text{HCOOH}$ , is a colorless liquid having a very pungent odor. It boils at  $100.7^\circ \text{C}$ ., melts at  $8.4^\circ \text{C}$ ., has a density  $d_{20/4}$  of 1.22026, and an index of refraction  $n_{20/D}$  of 1.37137. It is miscible with water, alcohol, and ether. Formic acid was first prepared by S. Fisher in 1670 by distilling crushed ants with water (*L. formica*) and from this it derives its name. The stings of some insects and plants also contain it, although the real poison is very likely a much more complex substance. Formic acid is different in chemical behavior from the typical carboxylic acids in that it exhibits not only the character of a monobasic acid but also that of an aldehyde. Formic acid has a strong bactericidal action resembling that of formaldehyde, probably due to its aldehyde charac-

ter. It is manufactured by the reaction between carbon monoxide and pulverized sodium hydroxide at moderate temperatures and pressures, followed by treating the resulting sodium formate with sulfuric acid to form formic acid. Formic acid is distinctly more acidic than other similar acids and the dissociation constant is about 12 times that of acetic. Formic acid decomposes to carbon dioxide and hydrogen when heated (in a closed system) at moderately elevated temperatures somewhat above the boiling point.

#### Industrial Uses

Formic acid is used in the textile and rubber industries as an inexpensive acidifying agent in place of acetic or sulfuric acid. In the chemical industry it is utilized in the manufacture, among other substances, of formates, organic esters, oxalic acid, and allyl alcohol. During 1954, formic acid amounting to 14,431,000 pounds was manufactured in the United States. Formic acid is used as a decalcifier, a reducer in dyeing wool, for dehairing and plumping hides, for tanning, electroplating, and as a fumigant and insecticide. Among other uses it has been employed as an antiseptic in the brewing industry and as a food preservative. Medical use is made of the salts of formic acid as diuretics, astringents, and counter-irritants.

#### Toxicity

Formic acid resembles acetic acid but it is more volatile, more irritant, more antiseptic, more resistant to oxidation, and when given in large quantities is said to induce nephritis. On oral administration in dilute form, formic acid behaves almost quantitatively like acetic acid. Water containing 0.001 to 0.25 per cent of either formic acid or acetic acid administered to rats for many weeks in daily dosage up to 0.2 milliliter of acid per kilogram of body weight (equivalent in man to 6 liters of 0.2 per cent per day) produced no effects whatsoever (1). Twice this amount fed to rats interferes materially and progressively with growth and appetite and is similar in this respect to acetic acid. Formic acid is irritating to the mucous membranes of the eyes, nose, and throat, and the concentrated acid when



splashed on the skin produces painful burns which are slow in healing. From feeding experiments by Wöhlbier and Siebert (2) in which guinea pigs were fed as much as 4 per cent of the dry weight of their feed of formic acid and/or calcium formate, it would appear that formate in these concentrations is quickly oxidized in the animal body. Measurements of the nitrogen balance, basal metabolism, and urinary hydrogen ion concentration of the animals showed no significant acidosis resulting from the ingestion of calcium formate. Since 1936, 34 cases of fatal poisoning by formic acid, most of which were suicidal in nature, have occurred in Travancore (3). The occurrence coincided with the development of the local rubber industry in which formic acid is used for coagulating the latex.

### Analysis

Atmospheric samples, in those cases where formic acid occurs as an aerial contaminant, may be obtained by bubbling a known volume of the air through fritted glass bubblers containing water made slightly alkaline with sodium hydroxide. The formic acid content may be determined colorimetrically with fuchsin reagent following the reduction of formic acid to formaldehyde with magnesium (4). A micromethod for the determination of less than 3 milligrams of formic acid has recently been developed by Khinoi (5).

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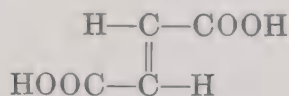
## FUMARIC AND MALEIC ACIDS AND MALEIC ANHYDRIDE

### Characteristics

The increasing use of fumaric acid, particularly in the plastics and resins indus-

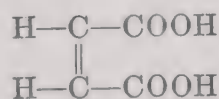
tries, has raised the question of toxicity, especially since its stereoisomer, maleic acid, is reputed to be toxic. The close relationship and industrial applications of fumaric and maleic acids and maleic anhydride make it desirable to group these substances together.

Fumaric acid, *trans*-ethylene-1,2-dicarboxylic acid, *trans*-butenedioic acid, *allo*-maleic acid, or *boletic* acid



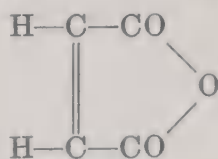
occurs in many plants, specifically in *Fumaris officinalis*, in Iceland moss, and in members of the boletus family. It is manufactured either by the fermentation of dextrose, or by the catalytic oxidation of furfural with sodium chlorate in the presence of vanadium pentoxide catalyst. Although it is but slightly soluble in cold water (0.63 gram per 100 grams at 25° C.), it may be crystallized from hot water. It is somewhat soluble in alcohol and in ether, but is practically insoluble in other organic solvents. It melts at 287 to 300° C. in a closed capillary, but sublimes from an open vessel at about 200° C. Above this temperature in the open it decomposes with partial carbonization into maleic anhydride and water. Its density is 1.625.

The stereoisomeric unsaturated dicarboxylic acid—maleic acid, *toxic* acid, or *cis*-butenedioic acid



is a synthetic product made by the catalytic oxidation of benzene over vanadium pentoxide. Maleic acid is a white, crystalline solid with a faint acidic odor. It melts at 135° C. and boils at 160° C. with decomposition partly into fumaric acid above this temperature and partly into maleic anhydride and water. Its density is 1.59. It is very easily soluble in water, but is only slightly soluble in organic solvents other than alcohol. It is characterized by a peculiarly disagreeable, nauseous taste.

## Maleic anhydride, toxilic anhydride



occurs in crystalline form with a melting point of 57 to 60° C. and a boiling point of 196 to 200° C. It sublimes easily, is readily soluble in water with the formation of maleic acid, and is somewhat soluble in chloroform, in ether, and in acetone, but is only slightly soluble in petroleum ether.

Fumaric acid is a natural product widely distributed in nature in cryptogams and phanerogams and was first obtained by fermentation in small yield by Ehrlich in a mold metabolic product using *Rhizopus nigricans*, and later by Wehmer (1) in the fermentation of sucrose with *Aspergillus fumigatus* in the presence of oxygen which gave large yields of the acid. This characteristic type of fermentation, however, is gradually lost and replaced by the production of gluconic acid. Gottschalk (2) found that the mold *R. nigricans* produced fumaric acid from pyruvic acid in the presence of excess chalk. More recently the commercial production of fumaric acid by new and efficient fermentation processes from starch and other carbohydrates has lowered the cost of production considerably (3).

## Uses

Maleic acid, maleic anhydride, and fumaric acid (which does not form an anhydride) constitute some of the major raw materials at present used in the synthetic resin industry. Fumaric acid and its esters yield resins with many desirable properties either by polymerization, or by copolymerization with, for instance, vinyl compounds or diethylene glycol. These resins are used in the field of paints and varnishes and as molding and casting resins. The production of fumaric acid in the United States in 1948 was 2,691,000 pounds (4), while the estimated production of maleic anhydride in this country in 1950 was 15,978,000 pounds. Production of fumaric acid had increased to 4,655,000 pounds by 1951, while maleic

anhydride production was 23,718,000 pounds in 1951 (5).

## Toxicity

Fumaric acid differs from maleic acid and maleic anhydride in that it is physiologically inert. Fumaric acid is converted into lactic acid by the action of a carboxylase secreted by yeast and when fumaric acid is fed to phlorhizinized dogs it is converted into dextrose (6). On the other hand maleic acid is entirely unattacked by yeast and not only is not converted into sugar in the body, but acts as a poison. The toxic effects of maleic acid have been attributed to its failure to be converted into lactic acid and dextrose in the animal body. Furthermore maleic acid is said to be a skin irritant (7). Maleic anhydride is especially hazardous, as direct contact with the skin causes burns. Furthermore the vapors or fumes are irritating to the respiratory tract.

## Analysis

Various methods have been proposed for the analytical determination of fumaric and maleic acids, as well as for maleic anhydride. However, none of these is specific. Most of the methods depend upon estimation of total acidity, or upon an halogenometric method, such as bromination. Both copper and lead fumarate crystals are said to be sufficiently characteristic for the microchemical identification of fumaric acid.

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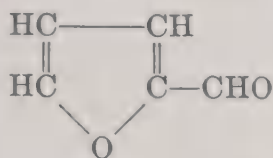
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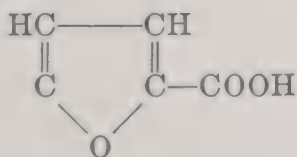
## FURFURAL

### Characteristics

Furfural, furfuraldehyde, furol, pyromucic aldehyde, artificial oil of ants, is a



colorless, mobile liquid which changes to reddish-brown upon exposure to light. It boils at 161.7° C., melts at -36.5° C., has a specific gravity of  $d_{20/4}$  1.1598, an index of refraction  $n_{20/D}$  of 1.5261, and a flash point of 55 to 58° C. Its solubility in water is approximately 8 per cent at room temperature. Furfural is miscible with alcohols, ethers, and most organic solvents with the exception of the paraffin hydrocarbons. It dissolves gums and resins, waxes, oils and dyes, most cellulose esters and ethers, and many organic substances. First made by Döbereiner in 1830, it is now manufactured on a large scale from agricultural wastes—particularly oat hulls and cotton seed hulls. The pentosans of these raw materials are hydrolyzed to pentoses and dehydrated to the aldehyde by subjecting seed hulls to the action of steam and dilute sulfuric acid while the mass is agitated in digesters. Furfural is separated from the distillate by fractionation. Furfural is readily volatilized with steam. As it is an aldehyde, it yields a crystalline addition compound with a saturated aqueous solution of sodium bisulfite and reduces such reagents as Tollen's and Fehling's solutions. With phenylhydrazine, furfural yields furfural phenylhydrazone, m.p. 97–98° C. Oxidation of furfural yields



(furoic acid). While its odor is unpleasant in concentrated form, when dilute furfural has the pleasant odor of new bread, in which indeed it is present.

### Industrial Uses

Furfural is used in the manufacture of several different types of resins and plasticizers. It is also used as a solvent in certain lacquers having a cellulose ester, cellulose ether, or varnish gum base; as a solvent or diluent for such substances as formaldehyde, oleic acid, and diphenylaminechloroarsine; in the purification and bleaching of organic compounds, and as a fly-repellent, preservative, fungicide, herbicide, and tanning agent (1). In the synthetic rubber industry, furfural is used as a selective solvent for the purification of butadiene. As a selective solvent, it is also employed in refining lubricating oils in the petroleum industry. Its solvent and penetrating properties make it a valuable component in dyeing mixtures for wood, shoes, textiles, and other such substances. Furfural is also useful in numerous organic syntheses.

### Toxicity

Furfural vapor is an irritant to mucous membranes and is a central nervous system poison, but because of its low volatility its toxic effect in general is slight. Ingested furfural has been shown to produce liver cirrhosis in rats (2) when added in amounts of 50 milliliters per kilogram of rice. Joachimoglu and Klissiumis found that furfural had 63 times the narcotic effect of ethyl alcohol on gold fish (3). Gander (4) found that injection doses greater than 0.3 milliliter caused convulsion seizures and paralysis in rabbits. In animals dying immediately, no changes in the ganglion cells could be demonstrated, but with repeated injection of 0.2 milliliter of furfural over a period of 11 days, there was extensive ganglion cell degeneration. Animal inhalation experiments have shown that breathing a concentration of 280 parts per million results only in slight irritation of the mucous membranes (5), while increasing the concentration 10-fold causes more acute irritation and results in dyspnea, prostration, paralysis, and cramps, with an acute lung edema. No industrial poisoning has been reported among workers handling this substance and Flury and Zernik (5) minimize the danger of acute

effects resulting from exposure, owing to the slight volatility of furfural. However, the possibility of chronic effects, such as nervous disturbances, following continued exposure should receive attention.

### Analysis

Furfural may be determined quantitatively with bromine by adding a measured excess of 0.1 normal concentration of potassium bromate in the presence of potassium bromide and 3 per cent hydrochloric acid. The furfural combines with 1 molecule of bromine and the excess of oxidant may be determined by adding potassium iodide and titrating with standard sodium thiosulfate solution (6). Very small amounts of furfural may be determined colorimetrically with orcinol (7) or by the use of 2,4-dinitrophenylhydrazine (8). In determining the absorption spectra of 2-furaldehyde in the vacuum ultraviolet, Walsh (9) found that strong absorption occurred in the region 2000–2700 Å, and that absorption maximum was in the region of 2600 Å.

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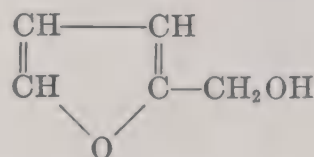
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## FURFURYL ALCOHOL

### Characteristics

Furfuryl alcohol, 2-furylcarbinol, 2-furancarbinol, α-furylcarbinol, 2-hydroxy-

methylfuran



is a colorless liquid having a boiling point of 170 to 171° C. (75.7° at 15 millimeters), a density of  $D_{23/4}$  1.1282 and an index of refraction of  $n_{23/D}$  1.48515. Furfuryl alcohol is miscible with water but the aqueous solution decomposes on standing. It is very soluble in alcohol and in ether. Furfuryl alcohol is prepared by the catalytic reduction of furfural using a nickel, chromium and copper catalyst, or by the action of a 30 per cent solution of sodium hydroxide on furfural in the cold. There is simultaneous production of furoic acid in the latter reaction. The oil obtained by the steam distillation of roasted coffee bean meal contains up to 50 per cent of furfuryl alcohol after the organic acids have been removed and the abundance of this constituent doubtless stimulated Erdmann's early investigation of "coffee oil" and the physiological effects of furfuryl alcohol (1). Furfuryl alcohol reacts with explosive violence with mineral acids and with some strong organic acids to form a black, brittle, insoluble, and infusible resin. It may be stabilized for storage by the addition of 0.5 per cent of urea. Furfuryl alcohol reduces permanganate in the cold.

### Industrial Uses

Furfuryl alcohol is used in the manufacture of resins and wetting agents and as a solvent. As furfuryl alcohol is toxic and is being produced commercially in large quantities, its hygienic significance is important.

### Toxicity

Erdmann (1902) found that furfuryl alcohol in small doses stimulates respiration in animals and man and that larger doses produce salivation, nausea, diarrhea, and diuresis. An investigation made much later by Joachimoglu and Klissiunis (2) on the stimulating effect of coffee and its constituents showed that there is an inhibitory effect of furfuryl alcohol on the isolated rabbit



intestine. Okubo (3) found that dilute solutions of furfuryl alcohol paralyze the sensory nerves. Gajewski and Alsdorf (4) found furfuryl alcohol to paralyze skeletal muscle and that death in such animals as the dog, rabbit, and rat is the result of respiratory paralysis. In a recent study by Fine and Wills (5), using rabbits and cats as experimental animals, it appeared that such cardiac effect as furfuryl alcohol exerts is that directly on the myocardium and that the conduction of impulses is not affected. The principal effect appears to be a central depressant action and death from furfuryl alcohol probably results from central respiratory depression. The presumptive lethal dose for the rabbit was found to be 0.7 gram per kilogram of body weight. Comstock and Oberst (6) report 25 per cent of deaths of rats after an 8-hour exposure to 700 parts per million of furfuryl alcohol, but no significant toxic effects were noted at an exposure of 19 parts per million for 6 weeks. The major end product when furfuryl alcohol is fed to rats has been found by Paul and his associates to be furoylglycine (7). Despite its somewhat toxic character no industrial disabilities appear to have been reported from contact with furfuryl alcohol.

### Analysis

Haslam and Ruddle (8) have found cerous sulfate reduction to be an accurate means of estimating small amounts of furfuryl alcohol. It has also been found that furfuryl alcohol gives a color with Dische's reagent (a mixture of diphenylamine with acetic and sulfuric acids). A characteristic absorption band at 5,800 angstrom units occurs when this reagent reacts with the alcohol (9). A simple color test for furfuryl alcohol is to moisten a pine shaving with it and add hydrochloric acid, which then produces a blue-green color.

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## HYDROCARBONS, SATURATED— PARAFFINS

### Methane, Ethane, Propane, and Butane

The first four members of the paraffin series of hydrocarbons, *i.e.*, those having from 1 to 4 carbon atoms, are gaseous at ordinary temperatures; those which follow, up to and including the sixteenth, are liquid; those higher than this are solid. The boiling and melting points are dependent on the size of the molecule since both increase with increasing molecular weight. The specific gravity also increases slowly with the molecular weight. The paraffins are inactive chemically as is shown by their inertness toward concentrated sulfuric acid and cold fuming nitric acid. The physical properties of methane, ethane, propane, and *n*-butane, all colorless gases, are enumerated in Table 8.

While methane and ethane are odorless, the odor of these hydrocarbons becomes more apparent as their carbon content increases. However, none of the gases referred to above has sufficient odor to give warning of its presence in the air in dangerous concentrations. The four hydrocarbons enumerated above occur as mixtures of gases evolved from oil or gas wells. Methane alone may be found in coal mines where it is designated as "fire damp" and it also originates from the decomposition of carbonaceous material in marshy places and is then designated as "marsh gas".

TABLE 8  
*Normal Saturated Hydrocarbons*

Substance	Formula	Boiling Point °C.	Meltint Point °C.	Density	Solubility (Cubic Milliliters per Liter of Water)
Methane	CH <sub>4</sub>	-161.7	-182.6	Liq. 0.416 <sup>-164°</sup>	90 <sup>20°</sup>
Ethane	C <sub>2</sub> H <sub>6</sub>	-88.6	-172.0	Liq. 0.446	47 <sup>20°</sup>
Propane	C <sub>3</sub> H <sub>8</sub>	-42.2	-187.1	Liq. 0.535	65 <sup>18°</sup>
Butane	C <sub>4</sub> H <sub>10</sub>	-0.5	-135.0	Liq. 0.60	150 <sup>17°</sup>

Although methane has little or no commercial application, it is used to some extent in organic syntheses. Ethane, propane, and butane, on the other hand, are used in refrigerating systems for the production of low temperatures, while propane and butane have extensive application as fuel for household and for many industrial purposes either alone or in mixtures. The term "liquefied petroleum gases" is usually used to designate any one of these substances or mixture thereof used for heating purposes.

These substances are of little toxicological interest, although they have frequently caused injury and fatalities from explosions, particularly in the case of methane, in coal mines. The physiological response to inhalation of the saturated hydrocarbons is that of asphyxiation. The slight narcotic effect noted in the lower members increases slowly with increasing molecular weight. The narcotic action of methane is produced only by inhalation under pressure. Ethane was found by Nuckolls (1) to produce slight drowsiness and irregular respiration but no other ill effects in concentrations of 4.7 to 5.5 per cent by volume with exposures of 2 hours' duration. Exposure to propane produced a slightly greater effect than ethane and, in the case of butane, exposure for 30 minutes to 5.0 to 5.6 per cent by volume caused slight stupor, irregular respiration, and some depression. In general, it may be stated that the fire and explosion hazard involved in the handling and the use of these hydrocarbons far outweighs their toxicological importance.

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### HYDROCARBONS, SATURATED— PARAFFINS

#### Pentane, Hexane, Heptane, and Octane Characteristics

The saturated hydrocarbons represented by the four substances designated above are members of singly linked carbon atoms, having the general formula C<sub>n</sub>H<sub>2n+2</sub>. These four members are liquids and are not very reactive chemically. This stability extends to reaction with such very reactive substances as fuming nitric acid and even chromic acid which has very little effect on them in the cold. When heated, however, they are generally oxidized to carbon dioxide and water. The isomers in general are more easily attacked than the normal paraffins. While no isomers are possible for the first three members of the paraffin series owing to the equivalence of the four valences of carbon, in the case of pentane three isomers are possible; hexane has six isomers; heptane nine isomers, and octane eighteen isomers. They may be prepared synthetically by a variety of processes, but occur naturally in the distillate from a number of organic substances and are principally obtained from petroleum. The paraffins are not absorbed by bromine in the cold or by sulfuric acid and in this way may be distinguished and separated from the unsaturated hydrocarbons. These hydrocarbons are insoluble in water, but are to some extent soluble in alcohol and are freely soluble in ether and a number of organic solvents. The physical char-



TABLE 9  
*Normal Saturated Hydrocarbons*

Substance	Formula	Boiling Point °C.	Melting Point °C.	Density $D_{20/4}$	Index of Refraction $n_{20/D}$
Pentane	$\text{CH}_3(\text{CH}_2)_3\text{CH}_3$	36.1	-129.7	0.62632	1.35769
Hexane	$\text{CH}_3(\text{CH}_2)_4\text{CH}_3$	68.8	-95.5	0.65945	1.37506
Heptane	$\text{CH}_3(\text{CH}_2)_5\text{CH}_3$	98.4	-90.66	0.68376	1.3877
Octane	$\text{CH}_3(\text{CH}_2)_6\text{CH}_3$	125.59	-56.90	0.70279	1.39760

acteristics of the above normal hydrocarbons are summarized in Table 9.

### Industrial Uses

Pentane and heptane have been used to some extent as anesthetics, while hexane and, to a less extent, octane are chiefly used for solvent purposes. These substances in addition to industrial importance as solvents are used for a variety of purposes, such as their employment in laboratories, their use in ice manufacture, and for filling low temperature thermometers.

### Toxicity

Pentane, hexane, heptane, and octane, the four members of the saturated hydrocarbon series enumerated above, are of very little toxicological interest. They produce narcotic effects especially noticeable in the lower homologues and, as the carbon content increases, show some irritant properties. According to Henderson and Haggard (1), exposure to pentane for 10 minutes at 5,000 parts per million produces no symptoms, while hexane produces dizziness in the same period of time at the same concentration, and heptane at 5,000 parts per million within 4 minutes produces marked dizziness, muscular incoordination, and emotional disturbances. Owing to their low solubility, these hydrocarbons are rapidly eliminated from the body when inhalation is discontinued and no accumulation occurs.

### Analysis

No method of analysis specific for any one of these saturated hydrocarbons has so far been proposed applicable to the determination of the substance as a aerial contaminant. Where the nature of the contaminant is known, it is possible to evaluate

its concentration within certain limits by adsorption on silica gel or activated charcoal, or by using a methane detector, providing the latter is calibrated for the specific hydrocarbon sought.

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## HYDROCARBONS, UNSATURATED

### Acetylene

Acetylene,  $\text{CH}\equiv\text{CH}$ , the first member of the alkynes which have the general formula  $\text{C}_n\text{H}_{2n-2}$  and the only member of the whole series of industrial importance, is a colorless gas which boils at  $-83.5^\circ\text{C}$ ., has a specific gravity of 0.613 ( $-80^\circ\text{C}$ .) as a liquid and 0.906 (air = 1) as a gas. Solid acetylene vaporizes without melting, since the boiling and melting points are so nearly alike. The pure gas is almost odorless and the odor of the technical product is due to traces of impurities, such as hydrogen sulfide, phosphine, etc. Acetylene is formed when a Bunsen burner strikes back and burns at the base and it is probable that the acetylene formed is due to thermal dissociation of ethylene. Acetylene is prepared on a large scale by the action of water on calcium carbide. It burns with a luminous, sooty flame and when mixed with air is exceedingly explosive. The limits of composition of the explosive mixtures are wide since only those mixtures containing less than 5 per cent or greater than 80 per cent of acetylene are not explosive. Acetylene is more soluble in water and other solvents than ethylene and

much more soluble than methane. One volume dissolves about 1.1 volumes of acetylene at room temperature. Acetone dissolves about 300 times its volume under 12 atmospheres of pressure and use is made of this property for the storage and handling of acetylene. Owing to its high degree of unsaturation, acetylene has a strong tendency to polymerize and is very reactive chemically with the formation of addition compounds. Thus, it combines directly with chlorine to form dichloroethylene,



Moist acetylene attacks various metals, such as zinc, lead, brass, copper, and nickel. It combines directly with the metals forming acetylides, such as  $\text{C}_2\text{Ag}_2$  and  $\text{C}_2\text{Cu}_2$  which are explosive when dry.

It is generally believed that explosions in the pure oxygen pot of rectifying columns producing oxygen from liquid air are attributable to acetylene. Acetylene may be present in the crude air or may be formed from the breakdown of the lubricating oil in the air compressor. As oxygen boils at  $-183^\circ \text{C}$ ., and acetylene freezes at  $-81^\circ \text{C}$ ., nearly all the acetylene entering the column will remain there, according to McKoon and Eddy (1), and from the standpoint of safe operation, it is necessary to determine the presence of traces of acetylene in liquid oxygen.

Acetylene is an important commercial source of a number of organic substances which are synthesized from it, such as acetic acid, acetone, alcohol, chloro derivatives, butadiene, and various polymerization products. While acetylene was formerly of great importance as an illuminant at the present time it is used for this purpose principally only in mines and in bicycle lamps. The oxyacetylene flame is used for the autogenous welding of metals. Acetylene is extensively used for the production of acetylene black which was produced to the extent of 7,583,370 pounds in 1945. The total production of acetylene in 1944 amounted to 5,536,131 units of 1,000 cubic feet, 3,884,495 of which were used in chemical synthesis and the remainder for commercial purposes.

Acetylene is a simple asphyxiant and, according to Flury and Zernik, acts as a narcotic when administered with a sufficient amount of oxygen. It has no irritant action on mucous surfaces. Acetylene is not toxic *per se* but when the concentration is sufficiently high to reduce the available oxygen to a small amount, it may produce the usual symptoms of anoxia even to the point of complete asphyxiation with death by smothering. Death follows the inhalation of acetylene itself in a concentration of 500,000 parts per million when breathed for 5 to 10 minutes and following the inhalation of 100,000 parts per million when breathed from 1/2 to 1 hour. In man, the inhalation of acetylene has been shown to be followed by a period of excitement, then coma, cyanosis, weak and irregular pulse, and memory failure (2). These symptoms quickly disappear following rescue. Although commercial acetylene now contains very few impurities, it was formerly frequently contaminated with such gases as arsine, hydrogen sulfide, or phosphine, and exposure to this impure acetylene often assumed more serious consequences than is the case at present. Acetylene may be readily detected by its formation of copper acetylide in slightly ammoniacal solutions of copper salts which form a rose-red color or red precipitate depending upon the amount of acetylene present. Coulson-Smith and Seyfang (3) have utilized this reaction for the quantitative estimation of small amounts of acetylene in air. In the method developed by these investigators the depth of color is evaluated by matching it with the color produced by adding standard ferric alum solution to an excess of potassium thiocyanate. The results agree with 0.01 per cent of the volume of the sample. This method has been adopted with some modification by McKoon and Eddy (1), and later was further modified by Geissman and his associates (4).

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## HYDROCARBONS, UNSATURATED—OLEFINS

### Ethylene, Propylene, Butylene, Amylene, and Hexylene

Unsaturated hydrocarbons contain 2 atoms less hydrogen in the molecule than the paraffins and are represented by the general formulae  $C_nH_{2n}$  (olefins) and  $C_nH_{2n-2}$  (acetylenes). The group of olefins is thus named because of the oily substance obtained by the action of chlorine on ethylene gas. Like the paraffins the lower members of the olefin series with 2, 3, and 4 atoms of carbon are gases, those with 5 to 18 carbons are liquids and the higher homologues are solids. They are lighter than water in which they are only slightly soluble.

Ethylene, olefiant gas or ethene, is a colorless gas with a characteristic sweet odor and taste. It forms an explosive mixture with air at a concentration of 3 per cent. It has a lower explosive limit of 2.7 and an upper limit of 28.6. It is not very soluble in water, but 1 volume of alcohol dissolves  $3\frac{1}{2}$  volumes of the gas. Propylene, butylene, amylenes, and hexylene have properties somewhat similar to ethylene with

reference to their chemical reactivity. These olefins are found in small quantity in many types of petroleum, some of which, the Canadian oils for instance, are richer than others. The cracking of heavy hydrocarbons may be so directed that the unsaturated hydrocarbons of low molecular weight such as ethylene, propylene, and butylene may be produced. Ethylene is obtained from oil cracked in the vapor phase, from cracked natural gas, and from coke oven gas. The olefins may also be formed by the pyrogenic decomposition of other organic substances. Several basic methods of preparation have been described, some of which are only of academic interest. The more important are the removal of hydrogen halides from alkyl halides by passing the vapor over heated alumina or barium oxide. They may also be prepared by the removal of water from saturated alcohols derived from the paraffins. This removal of water can be accomplished by passing the vapor of the corresponding alcohol over heated alumina, graphite, or aluminum phosphate. Owing to their chemical reactivity, the olefins enter into addition and polymerization reactions freely. The halogen hydrides add readily and oxidizing agents attack these olefins easily. Finally, the olefins show a remarkable tendency to add on to metallic salts such as the chlorides of iron, platinum, and iridium. The physical properties of the first five members of the series are given in Table 10.

TABLE 10  
*Unsaturated Hydrocarbons*

Substance	Formula	Boiling Point °C.	Melting Point °C.	Density (Liquid)	Solubility (Milliliters per Liter of Water 0° C.)
Ethylene (ethene)	$CH_2=CH_2$	-102.4	-169.4	0.6100	256
Propylene (propene)	$CH_3-CH=CH_2$	-47.7	-185.2	0.6104	446
Butylene (butene-1)	$CH_3-CH_2-CH=CH_2$	-6.5	-130	0.6255	Insoluble
Amylene (pentene-1)	$CH_3-(CH_2)_2-CH=CH_2$	40.0	-138	0.6429	Insoluble
Hexylene (hexene-1)	$CH_3-(CH_2)_3-CH=CH_2$	63.5	-98.5	0.6747	Insoluble

Ethylene is used extensively to mature the color of citrus fruits, bananas, and melons, and in the blanching of celery, endive, and other vegetables. Furthermore, it has the property of accelerating the ripening of fruits and vegetables. It is also used as a welding fuel and in its pure state as an anesthetic. Ethylene is used in the synthetic manufacture of ethyl alcohol and was used in the production of mustard gas during the late war. All the olefins are useful for organic syntheses owing to the readiness with which they form addition products. An important series of valuable organic compounds has thus resulted.

None of the lower members of the olefin series is of any toxicological significance in low concentrations. Ethylene and propylene are inhalation anesthetics but are effective only in quite high concentrations (60 per cent or more) and for that reason are administered with oxygen. The high concentration required to produce physiological response causes the gas to act simply as an asphyxiant rather than an anesthetic unless sufficient oxygen is also present in sufficient amount to support life. The higher members of the series have a more pronounced anesthetic action than ethylene or propylene. Beginning with amylene there is irritation of the mucous surfaces which becomes more noticeable with the higher members of the series. In man, nausea, narcosis, and dizziness have followed the experimental administration of amylene and urinary blood and albumin have been noticed. Cramps and cyanosis and paralysis have followed administration of the higher members of the olefin series and the narcotic dose in the latter case approaches that of the toxic dose. Apart from any consideration of toxicity, the explosion and fire hazards of these substances are noteworthy.

## HYDROGEN CYANIDE

### Characteristics

Hydrogen cyanide, hydrocyanic acid, prussic acid,  $\text{HCN}$ , is a colorless, very volatile, gas or liquid having an odor somewhat

resembling that of bitter almonds. It is an insidious poison and since many people are unable to recognize its presence by odor, they are unaware of danger. The gas is lighter than air, and therefore rises rapidly and diffuses rapidly. At temperatures below  $26.5^{\circ}\text{C}$ ., It is a clear, colorless liquid. The specific gravity of the liquid hydrogen cyanide is 0.6970; of the gas, 0.9348. The boiling point of hydrogen cyanide is  $26.5^{\circ}\text{C}$ . It is prepared by the treatment of a cyanide salt with dilute sulfuric acid. The gas is very soluble in water and alcohol, but owing to the weakness of hydrocyanic acid, it does not redden litmus paper.

Hydrogen cyanide gas is effectively absorbed by alkali hydroxides, soda lime, silver oxide, and sodium bicarbonate solution containing iodine. Gas masks, especially designed, will give adequate protection against the concentrations used in fumigation for an estimated period of 1 to 4 hours. In general, the fumigation concentrations are less than 1 per cent. In addition to the use of liquid hydrogen cyanide, various absorption preparations are in use, such as Zyklon (liquid  $\text{HCN}$  absorbed in fullers earth),  $\text{HCN}$  Discoids (liquid  $\text{HCN}$  absorbed in wood fiber discs), and Saftifume briquets (a mixture which produces  $\text{HCN}$  and cyanogen chloride from sodium cyanide and sodium chlorate mixed with sand) (1).

Commercially, cyanides may be made by a circuitous route in which methanol reacts with carbon monoxide to produce methyl formate,  $\text{CH}_3\text{OOCH}$ . The latter is then converted to formamide ( $\text{HCONH}_2$ ) by reaction with ammonia and finally the formamide is dehydrated to hydrogen cyanide. When combined with the plant production of ammonia in which the by-product is carbon monoxide, the formamide process is unquestionably superior economically. At the present time, however, the most important commercial process for the production of hydrogen cyanide utilizes ammonia, metallic sodium, and coke (2).

### Industrial Uses

Hydrogen cyanide has important use in the manufacture of acrylonitrile, which is used for the production of oil-resistant syn-



thetic rubber and plastics. Hydrogen cyanide is used with acetone to form the intermediate acetone cyanhydrin necessary for the production of methacrylate resins. It has extensive use in fumigating flour mills, ships (3), foodstuffs, and manufacturing plants, as well as in the preparation of nitriles, the extraction and electroplating of gold and other metals, and the preparation of pigments. Although information regarding production of cyanides has been regarded as confidential since 1939, the value of cyanides produced in the United States in that year amounted to \$4,100,000. The imports for cyanide salts and mixture in 1944 amounted to 28,103,198 pounds.

### Toxicity

Hydrogen cyanide is one of the most lethal poisons known. It appears to act directly on cellular processes inhibiting or destroying oxidative ability. For this reason it is extensively used as a fumigant since it kills all insects and all higher animals. It is not, however, a bactericide. Since it inhibits oxidative processes, thus arresting the activity of all forms of life, the cyanogen compounds are true protoplasmic poisons. As it thus arrests internal respiration, cyanide poisoning is a form of asphyxia. Fifty milligrams injected under the skin is lethal to man and according to Vedder (4), "The lethal dose by respiration is usually believed to be less than the above and our figures confirm this view." According to Henderson and Haggard (5), 200 to 400 parts per million of hydrogen cyanide gas are rapidly fatal after exposure of 30 minutes and the maximum concentration allowable for prolonged exposure is 10 parts per million. Dust or fume concentration of cyanides was set at 5 milligrams (as CN) per cubic meter. Since cyanide is rapidly absorbed from the lungs, symptoms of poisoning occur very quickly. Initially, the exposed individual may notice headache, dizziness, weakness, irritation of the eyes, and finally, a sensation of chest constriction. The individual rapidly loses consciousness, respiratory irregularity follows, and finally, paralysis. The now standard antidotes for the treatment of cyanide poisoning are sodium nitrite and sodium thiosulfate admin-

istered by subcutaneous injection one after the other rather than together (5). According to Jandorf and Bodansky (6), the inhalation of amyl nitrite frequently suggested as an antidote for hydrogen cyanide gas poisoning is somewhat ineffective, although it revives animals exposed to low lethal doses of cyanogen chloride. The ineffectiveness of amyl nitrite treatment has also been emphasized by Paulet (7) who states that it is of no significant value in treating hydrogen cyanide poisoning. Howard and Hanzal (8) investigated the chronic toxicity to rats of food fumigated with hydrogen cyanide and containing 100 to 300 parts per million of the latter. They found no evidence of chronic toxicity in these animals during a 2-year feeding period.

### Analysis

Owing to the great toxicity of hydrogen cyanide and cyanides in general, and therefore the importance of detecting the presence of these substances and also their quantitative determination, numerous methods have been proposed, most of which are satisfactory in ordinary use. The cyanides may be converted to thiocyanates readily and estimation may be made on the basis of the depth of red color produced by ferric salts. Conversion of cyanides to Prussian blue has also been advocated as a method of colorimetric estimation. A quantitative test paper based on this reaction has been prepared (9). The benzidine and copper acetate test is very delicate and is also applied on test papers where hydrogen cyanide has been used as a fumigant (10). Cyanides also give a dark red color with alkaline picrate solutions, but since other reducing substances react similarly, this method is of doubtful value (11). A delicate means of estimating hydrocyanic acid is that of converting it to ammonia by alkaline hydrolysis in a closed system and estimation of the ammonia thus formed by means of Nessler's reagent (12). Taylor (13) has recently described a method for the determination of hydrogen cyanide in gas containing hydrogen sulfide. Robbie and Leinfelder (14) have developed a phenolphthalein technique applicable to the measurement of small amounts of cyanide

gas in air, and Lester and Ordnung (15) have developed a sensitive portable self-contained phototube colorimeter for cyanide determination. A micromethod based on the formation of Prussian blue has been developed for the determination of hydrogen cyanide in insect and plant tissue and has an accuracy of  $\pm 1.5$  per cent in the range of 0.05 and 0.3 milligram (16).

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## ISOPHORONE

### Characteristics

Isophorone, isoacetophorone, 3,5,5-trimethyl-2-cyclohexene-1-one



is an unsaturated cyclic ketone. It is a liquid with peppermint like odor and cooling taste, nearly insoluble in water but miscible with the usual lacquer solvents. Isophorone is an excellent solvent for many oils, fats, gums, and resins. It is easily volatile with steam. Owing to its low vapor pressure (0.3 millimeter of mercury at 20° C.), it evaporates slowly at room temperature. While isophorone does not form an addition compound with sodium bisulfite, it dissolves very slowly in liquid sulfur dioxide, forming 1,1,3-trimethyl-cyclohexanone-5-sulfonic acid-3. Isophorone boils at 215° C., has a density  $D_{20.5/4}$  0.9255, index of refraction  $n_{21.5/D}$  1.4789, freezing point -8.1° C., and flash point of 95° C. Since both a ketone group and double bond are included in the structure of isophorone, it is a useful substance in organic synthesis. As a typical ketone it will react with aldehydes, amines, hydrocyanic acid, and substituted nitrogen derivatives. The double bond permits the addition of halogens, mercaptans, and alkyl amines.

### Industrial Uses

Isophorone is a comparatively new solvent in the lacquer and plastic industry. Following its introduction in 1940, production rapidly increased and it is now generally recognized as one of the most powerful ketone solvents for nitrocellulose and one of the best known solvents for copolymer vinyl resins. Isophorone finds important uses in organic synthesis.

### Toxicity

Smyth and Seaton (2) concluded, after exposing guinea pigs and rats to single ex-



posures of air containing isophorone vapor, that although isophorone is four times as toxic as methyl isobutyl ketone for single exposures of several hours, its actual hazard is somewhat less than that of this compound because of its lower vapor pressure. The early symptoms of exposure of guinea pigs to isophorone vapors were those of eye and nose irritation followed by slight narcosis. Death, which usually occurred during exposure, was caused by narcosis or in a few cases by lung irritation. A concentration of 300 parts per million gave rise only to minor pathology after 24 hours' continuous exposure. A later investigation by these authors showed that isophorone acts chiefly as a kidney poison. No effect whatsoever was found on animals exposed to 25 parts per million (3). Silverman and his associates (4), however, found that 25 parts per million will produce irritation of eyes, nose, and throat of human subjects.

### Analysis

Since isophorone is a ketone, determination of its concentration as an aerial contaminant may be made by means of the iodine titration method used by Patty, Schrenk, and Yant in their studies of the physiological response of animals to ketone vapors (5). Kacy and Cope (6) have recently devised a colorimetric method for the determination of small amounts of isophorone in air. This method is based on the reaction of isophorone with phosphomolybdic acid. The resulting molybdenum blue product is measured spectrophotometrically.

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## KEROSENE

### Characteristics

Kerosene is derived from petroleum and represents the fraction boiling between 200 and 300° C. It consists of a mixture of petroleum hydrocarbons, largely aliphatic derivatives of the methane series of from 10 to 16 carbon atoms per molecule. Alkyl derivatives of benzene and naphthalene are present in smaller amounts. Kerosene varies in color from pale yellow to water-white and is an oily, mobile liquid of a characteristic, but not too disagreeable, odor. Its density is about 0.80 and flash point is 65 to 85° C. It is insoluble in water but miscible with other petroleum solvents. It may be deodorized and decolorized by washing with fuming sulfuric acid followed by washing with sodium plumbite. This clear and deodorized product is commercially available as Deobase. Until 1910 kerosene was the most important product of the petroleum industry, but the increasing demand for gasoline by the automotive industry and the wide extension of the use of gas and electricity soon relegated it to a lower position.

### Uses

Kerosene is used as an illuminating and heating oil, as a degreaser and cleaner, as a solvent, as fuel in tractors, and as a carrier for insecticides. Production in the United States in 1951 was 135,742,000 barrels.

### Toxicity

Although ordinarily regarded as somewhat physiologically inert, kerosene is known to cause local irritation and under certain conditions causes drowsiness, collapse, twitching of the muscles, and coma. It is known to cause damage to the heart, liver, and kidneys. Richardson and Pratt-Thomas (1) determined the toxic effects of kerosene in dogs and rabbits by intragastric,

intraperitoneal, intravenous, and intratracheal administration to laboratory animals. Intratracheal injection killed rabbits and dogs respectively in doses as low as 0.25 cubic centimeter per kilogram of body weight and 1.0 cubic centimeter per kilogram. Dosage of 35 cubic centimeters per kilogram of body weight by stomach tube was fatal for rabbits.

Because of its de-fatting action on the skin prolonged or frequent periodic contact of kerosene may be irritating and cause dermatitis. Although sensitization is possible, this is probably not due to kerosene itself, but to the aberrant proteins of the skin resulting from contact damage (2).

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### KETENE

#### Characteristics

Ketene, ketoethylene, ethenone, carbomethene,  $\text{CH}_2=\text{CO}$ , is the simplest possible ketone. It is a colorless gas of penetrating odor, boiling at  $-56^\circ\text{C}$ . and melting at  $-151^\circ\text{C}$ . It has an odor resembling both chlorine and acetic anhydride. Since ketene readily polymerizes, it cannot be shipped or stored in the gaseous state. Ketene was first prepared by Wilsmore in 1907 by the action of red-hot platinum wire in contact with acetone, acetic anhydride, and acetic ester. A more modern method of preparation consists in cracking acetone alone by a glowing grid of resistance wire. A steady output of ketene may be produced by means of such a ketene generator which provides for the condensation and return to the boiling flask of unacted upon excess of acetone. In addition to the pyrogenic decomposition of acetone, ketene may be prepared by the action of zinc on  $\alpha$ -bromo fatty acid bromides or by heating dialkyl malonic anhydrides. Ketene is soluble in alcohol or ether but is decomposed by water. The ketenes are very reactive substances. Ammonia converts them into acid

amides, hydrogen chloride into acid chlorides, and halogens into the  $\alpha$ -halogen-substituted acid halides (1). Ketenes are auto-oxidizable, and form at low temperatures, unstable, explosive peroxides with oxygen. Carbon suboxide,  $\text{O}=\text{C}=\text{C}=\text{O}$ , is included in the group of ketenes. This substance is formed by heating malonic acid and phosphorus pentoxide to 140 to  $150^\circ\text{C}$ . in a vacuum or by the action of zinc on dibromomalonyl dibromide. It possesses a very unpleasant smell resembling acrolein, boils at  $7^\circ\text{C}$ ., and burns with a sooty blue flame.

#### Industrial Uses

While ketene has long been recognized as an important acetylating agent in the laboratory, it has more recently become of industrial importance for acetylation in the manufacture of cellulose acetate. As an acetylating agent, it generally reacts with compounds having an active hydrogen atom. With ammonia, it reacts to yield acetamide. Because of its reactivity, it is now the starting point for the manufacture of a number of important industrial chemicals, such as acetyl salicylic acid and cellulose formate.

#### Toxicity

Ketene is markedly toxic and particularly affects the eyes and lungs. While ketene has for some time been known as an intolerable irritant, the first systematic investigation of its toxic effects was reported by Wooster and his associates in 1947 (2). These investigators found that ketene is as toxic as, and comparable in action to, phosgene. In experiments on mice, rats, cats, guinea pigs, and rabbits, it was shown that ketene acts locally on the upper respiratory tract, causing deaths from pulmonary edema and the consequent anoxia in the same manner as phosgene. Exposure to concentrations as low as 116 parts per million (0.2 milligrams per kilogram) for 10 minutes was fatal to laboratory animals. The ketene dimer (diketene) is much less toxic. Wooster and his associates regard it as obvious that rigorous precautions should be taken by any establishment generating this material. Treon *et al.* (3) have observed the physiological response of several species of animals exposed to ketene



vapor within the range of 25 to 1,500 parts per million for short periods of time. The toxicity of ketene appeared to be of the same order of magnitude as that of phosgene and, like the latter, its action on the respiratory system was delayed. According to Gomer (4), while cases of fatal poisoning had not been observed in the German chemical industry, a number of cases of eye and throat irritation, cough, and bronchitis have been observed in workers exposed to both ketene and diketene vapor. No safe working concentration value has so far been established.

### Analysis

Wooster (2) determined the concentration of ketene by connecting the generator (at the beginning and end of each animal exposure) to absorption bubblers containing standard alkali and measuring the time required for neutralization. Phenolphthalein was used as an indicator. Diggle and Gage (5) determine the ketene content of air samples by absorption in alkaline hydrazine, treatment with ferric chloride, and photoelectric measurement of the ferric acetohydroxamic acid complex.

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## MALATHION

### Characteristics

Malathion, malathon, S-(1,2-dicarbethoxyethyl) *o,o*-dimethyl phosphorodithioate, *o,o*-dimethyldithiophosphate of diethyl

mercapto-succinate is a yellowish, oily liquid which boils at 156 to 157° C. per 7 millimeters. It has a refractive index of  $n_{25/D}$  1.4985. The commercial product is a dark brown liquid and has a garlic-like odor. Its density is  $D_{25}$  1.23. Malathion dissolves in water to the extent of 145 milligrams per liter and is somewhat easily hydrolyzed at a pH above or below 7. It is miscible with most organic solvents.

### Uses

Because of its insecticidal potency and reduced mammalian toxicity in comparison with parathion, malathion is competing strongly with the latter as an agricultural insecticide.

### Toxicity

According to Hazleton and Holland (1) malathion is much less toxic to mammals than parathion. The ratio for inhalation with rats for experimental animals is 1:135. The acute signs of toxicity are characteristic of anticholinesterase activity, but the effect of malathion is much less than that of parathion. Chronic oral ingestion of 5,000 parts per million of malathion resulted in marked depression of cholinesterase levels, but retardation of growth was noted only at 20,000 parts per million. The  $LD_{50}$  value for mice injected intraperitoneally with malathion was approximately 450 milligrams per kilogram of body weight. Tousey (2) states that malathion is low in dermal activity as well as in chronic activity and that there is no problem of residues on foodstuffs. However, the Food and Drug Administration has established a tolerance of 8 parts per million on a wide variety of fruits and vegetables. The present acute oral toxicity value of malathion for rats obtained by various investigators ranges from 1,400 to 5,834 milligrams per kilogram with 1,400 milligrams per kilogram being a generally accepted value.

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## MESITYL OXIDE

### Characteristics

Mesityl oxide, isopropylideneacetone, methyl *iso*-butenyl ketone, 4-methyl-3-pentenone-2,  $(\text{CH}_3)_2\text{C}=\text{CH}\cdot\text{CO}\cdot\text{CH}_3$ , is a liquid of strong odor suggestive of mice and peppermint, according to Browning (1). It dissolves in water with difficulty but is miscible in both alcohol and ether. Its boiling point is 130° C., density  $d_{20/4}$  0.86532, index of refraction  $n_{20/D}$  1.44397, freezing point -46.4° C., vapor pressure 8.7 millimeters of mercury at 20° C., and flash point 32° C. When diacetone alcohol is dehydrated by adding a minute amount of iodine as a catalytic agent and this is followed by slow distillation, the somewhat more volatile mesityl oxide is distilled from the reacting materials. Although known as an oxide, this substance should preferably be designated as an  $\alpha',\beta$ -unsaturated ketone. Mesityl oxide combines with sodium bisulfite in saturated aqueous solution to give a quantitative yield of the sulfite addition compound from which the original mesityl oxide can be regenerated. Mesityl oxide decolorizes bromine water, reduces alkaline permanganate solution, and with alkali and iodine, yields iodoform. When boiled with a little sulfuric acid or alkali, mesityl oxide yields acetone.

### Industrial Uses

Mesityl oxide is an excellent solvent for cellulose esters and ethers, as well as many resins, oils, and fats. Its solvent power for nitrocellulose is fully equivalent to that of ethyl acetate but in its evaporation rate it resembles a heavy solvent. It has been especially used as a solvent for synthetic rubber and for some of the vinyl resins.

### Toxicity

Specht and his associates (2) found that when guinea pigs were exposed to mesityl oxide a progressive general narcosis occurred, which was characterized by depression of body temperature, the respiratory and heart rates, as well as the abolition of

corneal, auditory, and equilibratory reflexes. The depression of the various body functions was found to be directly proportional to the concentration of inhaled vapor. Smyth and his associates (3) investigated the physiological response of guinea pigs and rats to repeated inhalation of vapors of mesityl oxide. Groups of animals were given 30 8-hour exposures to controlled concentrations of mesityl oxide vapor ranging from 25 to 500 parts per million. In comparison with isophorone, the latter appears to have twice the cumulative toxicity of mesityl oxide. However, mesityl oxide is 30 times as volatile as isophorone. Consequently, when the two solvents are being used in the same way and in equal quantities, 15 times as much local ventilation would be needed for mesityl oxide as for isophorone to afford the same degree of protection against chronic toxic effects. At 50 parts per million, mesityl oxide has no effect whatsoever on animals.

### Analysis

In the analysis of the mesityl oxide vapor used in their animal experiments, Specht and his associates (2) used a modification of the iodine titration method developed by Patty, Schrenk, and Yant (4). For this purpose the contaminated air was sampled in a 1-liter flask, sodium hydroxide added, the flask cooled, a measured excess of standard iodine solution added, and after standing, the excess iodine back-titrated with sodium thiosulfate.

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## METHANOL

### Characteristics

Methanol, methyl alcohol, wood alcohol, wood spirit, wood naphtha, Columbian spirits, Colonial spirits, or carbinol,  $\text{CH}_3\text{OH}$ , is a colorless, clear, very mobile, inflammable liquid that is completely miscible with water, alcohol, ether, and with most organic solvents. The boiling point is  $64.65^\circ\text{C}$ ., the melting point is  $-94^\circ\text{C}$ ., the density is  $n_{20/4} 0.7915$ , and the index of refraction is  $n_{15/D} 1.33066$ . The flash point of methyl alcohol is variously stated as  $6^\circ\text{C}$ . and  $9.5^\circ\text{C}$ . Its odor is somewhat similar to ethyl alcohol and it possesses a burning taste. It is oxidized to formaldehyde with red-hot copper wire coated with oxide and also yields formaldehyde with potassium dichromate and sulfuric acid in cold dilute solution. Boiling with concentrated hydriodic acid yields the iodide (boiling point  $43^\circ\text{C}$ .). The acetate (boiling point  $57.1^\circ\text{C}$ .) and benzoate (boiling point  $199.6^\circ\text{C}$ .) are both liquids and not recommended for identification of methanol. When methanol is heated with soda lime, sodium formate is formed with the evolution of hydrogen, and when methanol is distilled over zinc dust it breaks down into carbon monoxide and water.

### Industrial Uses

Natural methanol is produced by neutralization of the products of hardwood distillation with lime and subsequent dilution with water, treatment with charcoal, and redistillation. Synthetic methanol is manufactured by passing a mixture of carbon monoxide and hydrogen at high pressure and elevated temperature over a catalyst. Production of the latter type steadily expanded throughout the late war period and the production of natural methanol has dropped in volume since 1941. In 1947, 539,698,232 pounds were produced synthetically and 16,401,191 pounds by hardwood distillation. By far the largest amount of methanol is used in the production of formaldehyde (430,326,694 pounds). Approximately 39 per cent is used in anti-freeze, 9 per cent as a denaturant, and 5 per cent is used as a solvent. Smaller amounts are used for the pro-

duction of synthetic indigo and other dyes, for rubber accelerators, as a general solvent in organic syntheses and in paints, varnishes, and paint removers. Production in 1954 amounted to 1,118,477,000 pounds.

### Toxicity

The widespread use of methanol in industry together with the known toxicity of this substance has been a frequent cause for comment (1, 2). The vapor of methanol causes stupor, dizziness, depression of the central nervous system, cramps, disturbances of the digestive organs and of the bladder, and acidosis. Cases of blindness due to the effect of methanol on the optic nerve have been reported in industrial workers exposed to high concentrations of methyl alcohol vapor. Individual sensitivity has been noted and varies within wide limits. The symptoms shown in less severe cases of poisoning are headache, nausea, vomiting, and irritation of the mucous membranes. It has recently been shown in experiments with rats which were fed methanol that 31 per cent of the total amount ingested was excreted through the respiratory tract in from 96 to 138 hours (3). The acute  $\text{LD}_{50}$  of methyl alcohol was found to be 15.5 milliliters per kilogram for rats (4). This value is double that commonly reported for ethyl alcohol. The chief pharmacological effect noted was that of depression of the central nervous system. Although methyl alcohol was less toxic than ethyl alcohol in single acute doses, it was more toxic when given in fractional doses over a period of time due to the slower rate of oxidation and excretion. The recovery from chronic poisoning always occurs very slowly. Mass poisoning from the ingestion of methyl alcohol has frequently occurred. The destructive physiological effect of methanol has been ascribed to its oxidation within the body with the resulting formation of either formic acid or formaldehyde which poisons the nervous tissue. According to Zatman (5), no oxidation of methanol to formaldehyde occurs in the presence of ethanol. Henderson and Haggard (6) calculate that with an exposure of 200 parts per million of methyl alcohol, which corresponds to 0.29 milligram per liter, a working man

of 70 kilograms would absorb into the body during a working day of 8 hours 0.870 gram of methyl alcohol. According to these authors, the concentrations of methyl alcohol appearing in blood, urine, or expired air on repeated determinations would be a better index of the safety of working conditions than a standard based on ventilation. The accepted exposure to this concentration would result in the accumulation and retention after exposure of 34.4 grams of methanol. Obviously many days and nights of continuous exposure would be required before these equilibrium values were reached.

### Analysis

Hine and his associates (7) have recently developed a colorimetric method for the determination of methanol in blood and other tissues which depends upon the acid dichromate oxidation of methanol. The detection and determination of methyl alcohol as an air contaminant usually depends upon its oxidation to formaldehyde and the colorimetric estimation of the resulting formaldehyde by means of Schiff's reagent. Various means have been adopted for carrying out this oxidation, of which Jephcott's (8) oxidation with potassium permanganate appears to be the most accurate. This procedure, which had previously been developed and modified by Chapin (9) for the detection and estimation of small amounts of methyl alcohol in solution, has been extended and applied to the determination of air samples (8). Rogers (10) has recently subjected this method to critical study, particularly with reference to the efficiency of methods used for collecting the samples from the contaminated air, and has found that the midge impinger has a collecting efficiency of approximately 92 per cent at atmospheric concentrations of 200 parts per million of methanol.

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## METHOXYCHLOR

### Characteristics

Methoxychlor, 2,2-bis(*p*-methoxyphenyl)-1,1,1-trichloroethane, 2,2-di-*p*-anisyl-1,1,1-trichloroethane is a white crystalline substance prepared by the condensation of anisole with chloral in the presence of sulfuric acid or aluminum chloride. It melts at 89° C. and a dimorphic form melting at 78° C. has been described. Its density is  $d_{25}$  1.41. Methoxychlor is practically insoluble in water, but is soluble in alcohol. It is somewhat less soluble in petroleum solvents than DDT. While more resistant to alkali than DDT, it is slowly dehydrochlorinated by this agent to 2,2-bis(*p*-methoxyphenyl)-1,1-dichloroethylene and is also subject to catalytic dehydrochlorination by heavy metals.



## Uses

As an insecticide methoxychlor is especially effective against the Mexican bean beetle and has the advantage of more rapid knockdown than DDT.

## Toxicity

Methoxychlor is much less toxic to warm-blooded animals than DDT and, in addition to being only 1/25 to 1/50 as toxic, is preferred for use on animals in dairy barns, as it is not accumulated in fatty tissues nor excreted in milk. According to Krister (1) methoxychlor ranks high as an insecticide and decomposes completely in the body with no storage in the tissues. Hodge and his associates (2) maintained rats on diets containing 0.0025 to 0.16 per cent of methoxychlor for 2 years without ill effects except slight retardation of growth at the highest concentration. Experiments with dogs fed 20 to 300 milligrams per kilogram per day similarly indicated no ill effects nor tissue damage. Similar results with rats were obtained by Haag (3) in ingestion experiments, although methoxychlor was found to be more toxic to rats than DDT when administered by inhalation in kerosene spray. However, methoxychlor has in general been found to be much less toxic than DDT and apparently is one of the safest of insecticides.

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## METHYL ACETATE

### Characteristics

Methyl acetate,  $\text{CH}_3\text{CO}_2\text{CH}_3$ , is a colorless, transparent, volatile, inflammable liquid having a fragrant odor and a pungent taste. It boils at  $56.32^\circ\text{C}$ . (1), has a density of  $D_{20/4}$  0.9274, an index of refraction  $n$

$D_{20/D}$  1.3617, is partly soluble in water (about 31.9 grams per 100 grams of water), and dissolves readily in the ordinary organic solvents. Its vapor pressure at  $30^\circ\text{C}$ . is 265 millimeters of mercury. Methyl acetate is derived from methanol by heating with acetic and sulfuric acids, followed by distillation.

### Industrial Uses

No recent figure for the production of methyl acetate in the United States is available. However, production in 1942 amounted to 1,960,000 pounds. The principal use for methyl acetate is as a solvent for nitrocellulose and other cellulose esters in the manufacture of artificial leather and plastics. It has some use in the manufacture of paints, varnishes, and lacquers and in the perfume industry. While used to some extent as a substitute for acetone in cellulose coating lacquers, it has the disadvantage of hydrolyzing too easily.

### Toxicity

Exposure to methyl acetate vapor causes some irritation to the mucous membranes of the eye and the upper and lower respiratory passages. There is an increased flow of saliva. Methyl acetate is more weakly narcotic than some of the higher homologues, such as amyl acetate. In animals, inhalation of amounts below the threshold limit for narcosis produces general poisoning and long-lasting after-effects. There is usually no recovery following deep narcosis. The blood changes observed in animal experimentation consist chiefly of an increase in red and white cells and an increased hemoglobin. Serious exposure results in injury to the blood vessels, pulmonary hemorrhages, and pulmonary edema. No fatal industrial poisonings have been reported. However, Duquenois and Revel (2) noticed ocular and nervous disturbances in workers exposed to this vapor. Inflammation of the eyes, nervous irritating phenomena, dyspnea, tightness of the chest, palpitation of the heart, and exhaustion were observed. It was suggested by these investigators that methyl acetate may resemble methyl alcohol in producing atrophy of the optic nerve.

## Analysis

There is no specific method for the determination of methyl acetate where it exists as an aerial contaminant. Samples may be drawn over activated charcoal or silica gel and the amount adsorbed determined by the increase in weight in those cases where other aerial contaminants are absent. Methyl acetate may also be absorbed in alcohol using fritted glass bubblers and the acetate content determined by refluxing with a known amount of standard sodium hydroxide solution, followed by back-titration.

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## METHYLAL

### Characteristics

Methylal, also known as formal, dimethoxymethane, formaldehyde dimethyl acetal, and methylene dimethyl ether,  $\text{CH}_3\text{—O—CH}_2\text{—O—CH}_3$ , the simplest of the group of acetals, can be prepared very simply by the interaction of formaldehyde and methanol catalyzed by dry hydrogen chloride, or even by calcium chloride. It is a clear, thin mobile liquid, lighter than water and soluble to the extent of about 1 part in 3 of water. Methylal boils at  $42.3^\circ\text{C}$ ., melts at  $-105^\circ\text{C}$ ., has a density of  $d_{20/4} 0.8608$  and refractive index of  $n_{18/D} 1.3589$ . Its odor is slightly pungent and taste is alcoholic. Methylal, unlike ethers, does not form peroxides on standing. It is perfectly stable except in highly acid and aqueous solutions. It is stable in the presence of alkaline to moderately acid (pH of 3) solutions.

### Uses

Until recently methylal was of little commercial interest; however, it is now available on a tonnage basis and its characteristics and excellent solvent properties have initiated a rapidly expanding program of

industrial applications. It is an active or latent solvent for a number of materials of industrial importance, such as nitrocellulose, cellulose acetate and propionate, ethyl cellulose, vinyls, and polystyrene, as well as natural gums, waxes, and resins. As an extraction solvent it is in many ways superior to diethyl ether. It has been found to be especially useful in the plastics and perfume industries, and has been useful as a special fuel in rocket and ramjet engines.

### Toxicity

In common with many other volatile organic substances, methylal has at various times been suggested as an inhalation anesthetic, but it was not until 1943 that Bacq and Dallemagne made a serious investigation of the anesthetic action of methylal (1). In that year Bacq and Dallemagne used methylal in some 22 surgical operations as an anesthetic, having found that it could be used safely for that purpose. They found that the after-effects were less than with either ether or chloroform. However, it produced anesthesia more slowly than ether and its effect was more transitory. In 1950 Weaver, Hough, Highman, and Fairhall (2) determined the acute and chronic toxicity of methylal with white mice and guinea pigs as experimental animals. Experimental investigation of the metabolism of methylal did not indicate that the path of methylal excretion was other than that of ordinary respiration. In view of Keeser's investigation of the metabolism of methanol (3), tests for formaldehyde and formic acid were made of the vitreous humor and urine. However, there was no indication of the presence of these substances in any case. It is possible, therefore, in view of the stability of methylal in neutral or alkaline media, that methylal is not hydrolyzed at the pH of the body tissue fluids. Animals exposed to high concentrations of methylal often developed severe fatty changes in the liver, kidney, and heart and inflammatory changes in the lungs. Lower concentrations generally produced no significant pathologic changes. The  $\text{LD}_{50}$  value for male laboratory animals was found to be 18,354 parts per million and the threshold appeared to be about 11,300



parts per million. It would appear therefore that a reasonable safe working concentration for workers continuously exposed to methylal vapor for an 8-hour working day would be 1,000 parts per million.

### Analysis

Air samples taken in the above investigation (2) were allowed to stand overnight following the introduction of 1 per cent hydrochloric acid. The solution was then made up to 100 milliliters with water, 10 milliliters of this diluted solution transferred to a 100 milliliter Nessler tube and made up to 100 milliliters with water followed by 5 milliliters of Schiff's reagent, and the color compared, after standing 10 minutes, with standards prepared under identical conditions.

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## METHYL BROMIDE

### Characteristics

Methyl bromide, monobromomethane,  $\text{CH}_3\text{Br}$ , boiling point  $4.5^\circ\text{C}$ ., melting point  $-93^\circ\text{C}$ ., and density  $d_{0/0}$  1.73, is a colorless noninflammable gas at ordinary temperature and pressure and possesses but very little odor. At ordinary temperatures, methyl bromide is approximately three and one-third times as heavy as air, an important point with reference to industrial exposure. While it is soluble in most organic solvents, it is usually stated to be insoluble in water. The methyl bromide of commerce, however, dissolves to the extent of 6 to 10 grams per liter of water at  $18^\circ\text{C}$ . (1). With cold water, methyl bromide forms a voluminous crystalline hydrate. Owing to the very slight odor of methyl bromide, no warning of danger may be apparent to workers engaged in handling this substance. The advantage of methyl bromide as an insecticide

against a wide variety of insects in all stages of insect life has led to its extensive application in the fumigation of fruits and vegetables (2, 3). Application was made of methyl bromide early in the war as a delousing agent.

### Industrial Uses

In addition to its general application as a fumigant for insecticidal purposes, methyl bromide is used as an intermediate in the chemical industry, as a refrigerant, and in fire extinguishers. Its value as a fire extinguishing agent appears to be due largely to its blanketing action because of its great density. Its use for this purpose has been somewhat discouraged, however, owing to the very toxic nature of methyl bromide. Rising from a rather small output before the war, the maximum production figures for the United States were 3,678,000 pounds for 1944. Methyl bromide is used as a low boiling solvent and for the preparation of methyl compounds in the manufacture of aniline dyes.

### Toxicity

Methyl bromide is a highly toxic material of insidious action and is comparable in this respect with such substances as chloropicrin and the cyanides. It is toxic to the skin, causing vesicular dermatitis and second degree burns (4); to the respiratory system, causing bronchitis, pneumonia, and pulmonary edema; to the alimentary system, causing gastrointestinal disturbances and hepatic disfunction; and particularly to the nervous system. Short exposures to high concentrations cause headache, dizziness, nausea, vomiting, weakness, and diplopia. This is followed by mental excitement, epileptiform convulsions, muscular tremors and spasms, mental confusion, and at times, acute mania. The most serious disturbances are those arising from its effect on the central nervous system. Clarke and associates (5) report four cases (two fatal) of methyl bromide poisoning which occurred as a result of leakage of the fire-fighting apparatus on a British warship. In view of the extremely toxic nature of methyl bromide, its use in fire extinguishers of any type is highly

questionable. Most authorities are in agreement with a maximum allowable concentration value of no greater than 20 parts per million in the air to which workers may be exposed.

### Analysis

Methyl bromide may be detected as an atmospheric contaminant by means of a halide flame detector, which is sensitive to concentrations as low as 50 parts per million. This method, however, suffers from the disadvantage of being nonspecific. Turner's method, (6) for the micro estimation of bromides, made by conversion to pentabromorosaniline, can be adapted to atmospheric impinger samples. Chlorides do not interfere. Methyl bromide in concentrations as low as 1 part per million may be determined by combustion in a quartz tube at 95° to 1000° C. and absorption of the combustion products in dilute sodium hydroxide (7). The bromine content of the sodium hydroxide solution is determined by the Kolthoff-Yutzy procedure (8). Russel (9) has developed a rapid method of determining small quantities of methyl bromide following fumigation with this substance.

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## METHYL CHLORIDE

### Characteristics

Methyl chloride, monochloromethane,  $\text{CH}_3\text{Cl}$ , is a colorless, liquefiable gas, having a faint sweet, ethereal odor. It is soluble in both water and in ethyl alcohol; boiling point  $-24.2^\circ\text{C}$ .; melting point  $-97.9^\circ\text{C}$ .; specific gravity 1.785 (air = 1). Its solubility in water at  $16^\circ\text{C}$ . is 280 milliliters per 100 grams of water. The commercial production of methyl chloride in this country is based either on the reaction of hydrogen chloride on methyl alcohol in the presence of a catalyst or by the reaction of chlorine on methane. In the latter process, dichloromethane, chloroform, and tetrachloromethane are also formed. Chlorine and methane in certain proportions form explosive mixtures and careful control of this process is required. In both methods of preparation, removal of corrosive impurities and moisture to very strict limits is required. Foreign production of methyl chloride includes another process which is based upon the decomposition of trimethylamine hydrochloride at  $360^\circ\text{C}$ . Methyl chloride can be hydrolyzed with calcium hydroxide to form methanol and this method of commercial methanol synthesis was proposed prior to the method finally adopted of direct synthesis from carbon monoxide and hydrogen.



### Industrial Uses

Because of its stability, relatively low boiling point, and the fact that it is relatively noninflammable, nonexplosive, and noninjurious to food, methyl chloride has to a large extent replaced ammonia and sulfur dioxide in refrigeration. It finds other uses, such as a dewaxing medium in petroleum refining, as a catalyst solvent in synthetic rubber production, and as a methylating agent in synthetic organic chemical production. During the war when the Freons were not readily available, methyl chloride was proposed and to some extent used in the aerosol technique of insecticide distribution. Methyl chloride is transported as a liquefied gas in cylinders for small users and in drums containing 1,200 pounds or in tank cars holding 24,000 to 36,000 pounds for large users (1). The production of methyl chloride, both crude and refined, in the United States in 1945 amounted to 29,702,000 pounds. Production in 1954 amounted to 33,147,000 pounds.

### Toxicity

Methyl chloride is broken down in the body into methanol and hydrochloric acid. The chlorides formed by the neutralization of the hydrogen chloride produced are of course of no importance toxicologically. The speed and extent of the preliminary breakdown of methyl chloride in the body are not known. However, the excretion of methyl chloride is very slow and occurs principally through the lungs. It would appear that the toxic action of methyl chloride is attributable chiefly to its function as a molecular entity. Methyl chloride is only a mild narcotic and the victim may be unaware of exposure to the gas over some period of time since it is nonirritating and is almost odorless. The symptoms of mild poisoning are characterized by a staggering gait, dizziness, and headaches, which are followed hours later by anorexia, nausea, and vomiting. The illness following moderate exposure may last for several weeks and is often characterized by such ocular symptoms as mistiness, diplopia, and difficulty in accommodation. Very serious cases are characterized by severe involvement of the central nervous system

and often by hepatic and renal damage and depression of bone marrow activity. The mortality is high and in those who survive some prolonged or permanent incapacity is not uncommon (2). Sayers, Yant, Thomas, and Berger (3) found that all animals exposed from 10 to 110 minutes to concentrations of from 9.5 to 15.3 per cent died 1 to 4 days later. Since methyl chloride is sometimes used in place of Freon gas for refrigeration and air conditioning and since methyl chloride has so little odor, acrolein is sometimes added to serve as a warning agent. McNally (4), however, reports eight cases of methyl chloride poisoning with three deaths as proof that acrolein is not an absolutely dependable warning gas for the highly toxic methyl chloride refrigerant. Smith and von Oettingen (5) state that daily exposures to concentrations of 500 parts per million are extremely dangerous even for a period of 2 weeks or less and recommend a maximum allowable concentration value of well below 500 parts per million for exposures of relatively long duration.

### Analysis

Methyl chloride is more readily decomposed than many other chloro-organic compounds encountered in industrial hygiene surveys, and most of the procedures adopted for the analysis of such substances are readily applicable to methyl chloride. It may be detected as an aerial contaminant by means of the halogen flame detector and may be quantitatively determined by decomposition with alkali in a pressure flask and subsequent estimation of the chloride found by means of a Volhard titration. Patty, Schrenk, and Yant (6) devised a combustion method for methyl chloride vapor in air which is adequate for determination of methyl chloride concentrations of the order of 50 parts per million. Timmis (7) has recently devised an apparatus suitable for the detection and estimation of small amounts of such chloro compounds in air. A recent method described for the determination of low concentrations of methyl chloride in air consists of passing a measured volume of the contaminated air through an electric spark between carbon electrodes and absorbing the

products of combustion in sodium arsenite solution. The solution is slightly acidified and the trace of chloride present is determined nephelometrically (8).

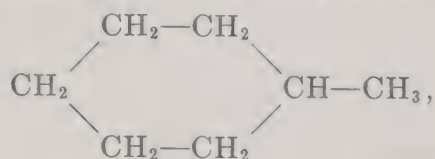
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### METHYLCYCLOHEXANE

#### Characteristics

Methylcyclohexane, hexahydrotoluene,



is a colorless liquid having a boiling point of 100.80° C., a melting point of -126.4° C., density  $D_{25/4}$  of 0.76512, and index of refraction of  $n_{20/D}$  1.42310. The lower limit of inflammability in air is 1.2 per cent by volume. Methylcyclohexane is insoluble in water but is miscible with many organic solvents. It is insoluble in methyl nitrite even at 23° C., but is soluble in benzyl alcohol at 30° C. Methylcyclohexane is not affected by concentrated sulfuric acid or by a mixture of nitric and sulfuric acids at room temperature. When treated with dry bromine with a trace of aluminum bromide, it is converted to pentabromotoluene, which

crystallizes in needles from benzene and has a melting point of 284° C. Methylcyclohexane is present in certain petroleum found in the Near East and may be separated by distillation. The catalytic hydrogenation of toluene produces methylcyclohexane and it may also be produced by causing benzene and methane to react at high temperatures.

#### Industrial Uses

Methylcyclohexane is chiefly used as a solvent and has certain properties which make it desirable as a co-solvent for cellulose ethers. It has limited application also for organic synthesis.

#### Toxicity

Lazarew (1) determined the amount of methylcyclohexane in air which would produce physiological response in white mice. With an inhalation period of 2 hours, this investigator found that 30 to 40 milligrams of methylcyclohexane per liter (7,500 to 10,000 parts per million) caused prostration and 40 to 50 milligrams per liter (10,000 to 12,500 parts per million) caused death. The minimum lethal dose administered by mouth for rabbits was found by Treon and his associates (2) to lie between 4 and 4.5 grams per kilogram. Severe diarrhea occurred, but no convulsions were noted. Repeated application of methylcyclohexane to the skin of a rabbit induced local irritation and thickening, but did not cause death. The irritation appeared on the second day and increased somewhat on successive treatments. A concentration of 4.57 milligrams of methylcyclohexane per liter of air (1,162 parts per million) appears to be innocuous for rabbits (2). Prolonged exposure to 372 parts per million appears to be harmless for monkeys. Deaths occurred amongst animals exposed repeatedly to concentrations of 28.75 milligrams per liter or higher. Narcosis occurs, general convulsions, and in the case of lethal concentrations, conjunctival congestion with mucoid secretion and lachrimation, salivation, coughing, sneezing, labored breathing, and diarrhea. The above investigators found increases in the rectal temperature of rabbits exposed to the highest concentrations and a slight fall in the daily rectal tempera-



ture after exposure to all lower concentrations. No industrial poisoning from exposure to methylcyclohexane has been reported.

### Analysis

No specific analytical method for the determination of methylcyclohexane as an atmospheric contaminant has been developed so far. It should be possible, however, to apply a properly calibrated combustion indicator to the determination of this substance when it is the sole organic atmospheric contaminant.

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## METHYLCYCLOHEXANOL

### Characteristics

Methylcyclohexanol, hexahydrocresol, hexahydromethylphenol,  $\text{CH}_3\text{C}_6\text{H}_{10}\text{OH}$ , molecular weight 114.18, is an anhydrous mixture of the three isomeric *o*, *m*, and *p* forms, each of which can exist in two geometric modifications. It is obtained by the hydrogenation of cresol, and since the commercial cresol is essentially a mixture of the *m* and *p* isomers of this substance, hydrogenation results in an admixture of the three isomers of methylcyclohexanol. The commercial product is a neutral, colorless, oily liquid having an odor resembling amyl alcohol, although weaker, and is but slightly soluble in water. Its boiling point range is 170 to 180° C. and density at 20° C. is 0.922. Its volatility is half that of cyclohexanol and its refractive index at 25° C. is 1.4580.

### Industrial Uses

Methylcyclohexanol has much the same uses as cyclohexanol but is not as powerful a solvent. It is used in soap manufacture, in the textile and artificial silk industry, as

a degreaser, and in the manufacture of isoprene rubber.

### Toxicity

Pohl (1) in 1925 found that on oral administration of methylcyclohexanol to dogs, cats, and rabbits the only noticeable effect was that of narcosis. When inhaled by animals he found it practically nontoxic. An examination by the British Home Office in the years 1933, 1934, and 1935 of workers using methylcyclohexanol proved the compound to be nontoxic though two workers at one time showed slight disturbance of the white cell count (2). Treon and associates (3) found the methylated series—methylcyclohexanone, methylcyclohexanol, methylcyclohexane—to be more toxic than the corresponding nonmethylated compounds when administered orally or when applied to the skin. Anesthesia developed rapidly following administration of both lethal and sublethal doses of methylcyclohexanol and likewise there was an increase in the glucuronic content of the urine. Repeated cutaneous application resulted in convulsive movements, narcosis, and death (minimum lethal dose for rabbits lies between 6.8 and 9.4 grams). Animals exhibited no evidences of discomfort or intoxication during periods of exposure to from 0.56 to 1.06 milligrams of methylcyclohexanol per liter of air. At 2.3 milligrams per liter, it caused irritation to the eyes of rabbits. No blood changes were observed in animals subjected to inhalation or to oral or cutaneous administration (3).

### Analysis

The concentration of methylcyclohexanol in air has been determined colorimetrically by Treon and associates (3, p. 327) by measuring the intensity of the straw color produced by its reaction with catechol and concentrated sulfuric acid. The sample is compared with a suitable standard in a 2-inch cell of a wedge photometer at 520 or 540 millimicrons. The acetyl value (the number of milligrams of potassium hydroxide required to combine with the acetic acid liberated from 1 gram of acetylated substance) for methylcyclohexanol is 492.

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## METHYLCYCLOHEXANONE

## Characteristics

Methylcyclohexanone, methyl anone,  $\text{CH}_3\text{C}_5\text{H}_9\text{CO}$ , is a neutral, colorless, somewhat viscous liquid with an odor resembling that of acetone. It has a molecular weight of 112.16, a density of 0.915, boiling point from 169 to 171° C., and a vapor pressure of 10 millimeters of mercury at 55° C. It is soluble in water to the extent of 2 to 3 per cent at 20° C. It closely resembles cyclohexanone in its physical properties and as solvents they are interchangeable. Since commercial cresol is essentially a mixture of *m* and *p* isomers, its hydrogenation to methylcyclohexanol and the partial dehydrogenation of methylcyclohexanol to methylcyclohexanone finds methylcyclohexanone also chiefly a mixture of the *m* and *p* isomers. Any one of the three methylcyclohexanones may be distinguished from the other isomers by dissolving it in concentrated hydrochloric acid. After standing at room temperature for 24 hours, the *o* compound is unchanged, the *m* crystallizes and the *p*-compound separates as a viscous oil. With benzaldehyde in alkaline solution, the *o* yields a yellow oil, the *m* from alcohol solution yields yellow crystals of melting point 122° C., and the *p* yields yellow crystals of melting point 98 to 100° C.

## Industrial Uses

Methylcyclohexanone is a solvent used in the manufacture of lacquers and varnishes and of plastics. It is used in the leather industry and as a rust remover.

## Toxicity

Methylcyclohexanone has an irritating effect on the mucous membrane. Repeated cutaneous application to the skin of rabbits produces hypothermia, narcosis, and convulsive movements. The minimum lethal dose when applied to the skin is between 4.9 and 7.2 grams per kilogram (1). Anesthesia and cyanosis develop rapidly following the oral administration to rabbits. In air the maximum concentration harmless for rabbits on prolonged exposure lies between 0.82 and 2.31 milligrams per liter. At 2.31 milligrams per liter, it irritates the eyes of the animals. Methylcyclohexanone does not cause narcosis within the limits of concentrations that can be obtained at ordinary temperatures. The decrease in the ratio of the inorganic sulfates and likewise the excretion of glucuronic acid in the urine of rabbits during exposure varies with the concentration to which the animals were exposed. No changes are observed in the blood of animals subjected to inhalation of these compounds.

## Analysis

Both cyclohexanone and methylcyclohexanone in air were determined colorimetrically by Treon and his associates (1) by measuring the intensity of the pink color produced by a reaction of the Zimmerman type, with *m*-dinitrobenzene. The resultant samples were compared with freshly prepared standards in the 2-inch cell of a wedge photometer at 540 millimicrons.

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## METHYL FORMATE

## Characteristics

Methyl formate,  $\text{HCOOCH}_3$ , is a colorless, inflammable liquid, having a boiling



point of 31.5° C., a melting point of -99.0° C., density of  $d_{20/4}$  0.97421, and an index of refraction of  $n_{20/D}$  1.344. It has a flash point of -32° C., a vapor pressure at 20° C. of 476.4 millimeters of mercury, is soluble in water, alcohol, and ether, and has an agreeable ethereal odor. The lower limit of inflammability of methyl formate is about 5 per cent and, at this concentration, it is readily detectable by odor and by its irritant properties. Methyl formate is made by heating methyl alcohol with sodium formate and hydrochloric acid, followed by distillation.

### Industrial Uses

Methyl formate is used as a fumigant and larvicide, as a reagent in making various organic and intermediate chemicals, and as a solvent for cellulose acetate.

### Toxicity

It would be anticipated that the vapors of the esters of organic acids would be to some extent hydrolyzed following absorption or contact with mucous surfaces and the skin, and that the acid and the corresponding alcohol would be liberated locally. In such cases, the chemical nature of the organic acid would determine the physiological response to absorption of the ester. On these grounds, methyl formate would be expected to be more irritating than the acetate. Methyl formate has been found indeed to have more irritating action than either methyl or ethyl acetate. Schrenk and his associates (1) found the symptoms occurring in guinea pigs exposed to methyl formate vapor to be, in the order of their appearance, nose and eye irritation, retching movements, incoordination, narcosis accompanied by incoordinated movement of the extremities, and death. Methyl formate vapor was especially irritating to the lungs. Whatever anesthetic effects were developed were stated to be due to the alcohol. The physiological responses for a single exposure indicated that 0.5 per cent is the maximum amount for 60 minutes' exposure without serious disturbances, and 0.15 to 0.20 per cent is the maximum amount for exposure for several hours without serious disturbances.

### Analysis

Methyl formate as an aerial contaminant was determined by Schrenk and his associates (1) by using air-equilibrated activated charcoal to adsorb the gas from a measured volume of the vapor-air mixture and then determining the gain in weight. It is necessary to remove the soda lime from the usual adsorption train as the latter causes hydrolysis of the methyl formate. Silica gel could also be substituted for activated charcoal in this determination and larger amounts of methyl formate could be determined by hydrolysis with standard alkali and titration with standard acid, or by hydrolysis and precipitation of silver formate from a neutral solution of silver nitrate.

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## METHYL IODIDE

### Characteristics

Methyl iodide, iodomethane,  $\text{CH}_3\text{I}$ , is a colorless, transparent, mobile, aromatic, sweet smelling, acrid liquid which turns brown on exposure to light. It boils at 45° C., melts at -66.1° C., decomposes at 270° C., has a specific gravity of 2.293 (18° C.), and an index of refraction  $n_{21/D}$  of 1.5293. It is miscible with alcohol and ether and is 1.4 per cent soluble in water. Methyl iodide is formed by the action of phosphorus tri-iodide in replacing the hydroxyl group of methyl alcohol or instead of using ready prepared phosphorus tri-iodide by mixtures of phosphorus, iodine, and methyl alcohol. It is also prepared by the interaction of dimethyl sulfate and sodium iodide and by the interaction of methyl alcohol, sodium iodide, and sulfuric acid with subsequent distillation.

### Industrial Uses

Methyl iodide is of special importance in organic syntheses, since its iodine atom is very reactive and since it is a liquid at room

temperature, which makes it easier to use than methyl chloride or bromide, which are both gases at that temperature. Besides its use in methylations, it is used in microscopy because of its high refractive index; as imbedding material for examining diatoms; and as a testing material.

### Toxicity

According to Garland and Camps (1), there is a striking resemblance between methyl iodide poisoning and poisoning with methyl chloride and methyl bromide. They report that Jaquet in 1901 recorded the case of a man who contracted methyl iodide poisoning while employed in a dyeworks (2). The symptoms were vertigo, diplopia, and ataxia, the patient swaying as if drunk. Chemical tests of the urine showed iodine to be present. Delirium and mania made treatment in a mental hospital necessary. Mental dullness persisted. An account is given by Garland and Camps of the case of a worker on the process of manufacturing methyl iodide in an open method where undoubtedly he was exposed to its fumes. He was found drowsy and unable to walk; the speech was slurred and incoherent. The muscles of the upper limbs twitched and the lower limbs were spastic. Only 1 pint of urine was passed in 24 hours; it contained 9 milligrams of combined iodine per 100 milliliters and no bromine or methyl alcohol. The patient died a week later. Chemical examination of the brain yielded a total of 6 milligrams of combined iodine. In 1940, Hunter, Bomford, and Russell recorded four cases of poisoning through inhalation of methyl mercury iodide in a factory for the production of fungicides (3). With the exception of tremor, the symptoms of poisoning by inorganic mercury were absent and the symptoms resembled much more those of the nervous system associated with methyl derivatives. Severe generalized ataxia, dysarthria, and gross constriction of the visual fields were present, while memory and intelligence were unaffected. Since methyl iodide has not always been regarded as dangerous, all workmen must be informed of the dangers associated with this material. Buckell (4) regards methyl iodide as at least

as toxic as methyl bromide and several times as toxic as carbon tetrachloride. The method of manufacture should be that of total enclosure and also adequate ventilation should be provided.

### Analysis

While no method for the detection and estimation of methyl iodide as an aerial contaminant has so far been devised, the development of a suitable procedure should present no difficulty to the industrial hygiene chemist. Methyl iodide is readily hydrolyzed. It gives a precipitate with alcoholic silver nitrate in the cold. With dimethylaniline, it rapidly forms trimethylphenylammonium iodide, which is volatile at 220° C. and which is soluble in cold alcohol (1 part in 90 parts of alcohol). It forms addition compounds with pyridine, having a melting point of 117° C., and with quinaline, melting point 72° C. In addition to the ease of hydrolysis with alkalis, which would permit the quantitative evaluation of small amounts of methyl iodide by iodine titration, methyl iodide readily forms addition compounds with tertiary amines. These derivatives yield fully ionized iodine in aqueous solution and the latter may be titrated with silver nitrate in neutral or acid solution.

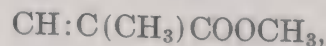
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## METHYL METHACRYLATE

### Characteristics

Monomeric methyl methacrylate,



is one of the more important esters of methacrylic acid. These esters are changed into resins by heat and light and such catalysts



as oxygen, ozone, and peroxides. Methyl methacrylate boils at 100.3° C. (76 millimeters of mercury), has a specific gravity 15.6°/15.6° of 0.950, a refractive index  $n_{15.6/D}$  of 1.414, and a softening temperature of 125° C. (1). The resin is unusually clear, is colorless, light, stable, hard, strong, high melting, and moisture resistant, as well as tough, inert, and thermoplastic. It has a density of 1.19 and a tensile strength of 7,000 to 9,000 pounds per square inch. In the manufacture of methyl methacrylate, acetone is converted to acetone cyanohydrin by reaction with hydrogen cyanide. This in turn is treated with methanol to form methyl methacrylate which by polymerization is transformed into the resin or plastic known by such names as Plexiglas (Rohm and Haas) and Lucite (duPont). A newer method of synthesis and polymerization originally developed for the Chinese government consists of the synthesis of dimethylhexine diol from acetylene and acetone, an ozone catalyzed oxidation-splitting of this substance to  $\alpha$ -hydroxy isobutyric acid and the esterification and dehydration of  $\alpha$ -hydroxy isobutyric acid with phosphorus pentoxide and methanol to form methyl methacrylate monomer (2)

### Industrial Uses

Polymethyl methacrylate and copolymers of methyl methacrylate and ethyl acrylate have achieved outstanding success in the form of cast sheets, rods, and tubes. Most of the applications of cast methacrylates are due to their unique optical properties for they possess a degree of transparency rivalled by no other plastic and excelled by few substances. The perfect clearness of methyl methacrylate resin and its ability to take a high polish make it useful in optical and illuminating devices based on the total reflection of light. Its most important use is in transparent airplane enclosures where its lack of scratch resistance is its greatest shortcoming. Other uses include edge-lighted instrument panels, pointers, and signs, curved dental, surgical, and industrial instruments for piping cool light to difficultly accessible locations, optical equipment, scientific instruments, display fix-

tures, decorative columns and rails, and miscellaneous novelties (1).

### Toxicity

The toxicity of the methacrylates was investigated by Deichmann (3) in 1941 and by Spealman and his associates (4) in 1945. Deichmann found that a concentration of 19 milligrams of methyl methacrylate per liter of air killed all exposed animals in 2.5 to 5 hours and that by oral administration 17 milliliters per kilogram of body weight was the minimal lethal dose for rabbits and rats. The symptoms resulting from exposure were accelerated respiration followed by a slowly developing motor weakness, decreased respiration, dyspnea, loss of reflex activity, and increased defecation and urination. The urine of rats usually contains hemoglobin while the blood porphyrin content is elevated in rabbits. Gross pathological changes are confined primarily to the respiratory system. Spealman and his associates, however, found the vapors of methyl methacrylate to be more acutely toxic for mice than those of acetone and less toxic than those of ethyl acetate. Guinea pigs were subjected to 39 milligrams per liter of methyl methacrylate gas for 3 hours daily for 15 days without untoward effects, indicating that the effects are not cumulative. At a concentration of 47.7 milligrams per liter, 9 out of 15 mice died in 5 hours. The estimated  $LD_{50}$  for mice exposed to these vapors for 3 hours is 55 milligrams per liter. The most characteristic histological changes in animals exposed for prolonged periods to high concentrations of methyl methacrylate vapors were degenerative changes in the liver. On local application to the skin of rabbits it caused a fleeting mild irritation. Instilled into the rabbit eye, it caused irritation which on occasion required several days for recovery. By the patch test method, about one-third of the subjects studied developed a mild initial erythema at the site of application. When tested 10 days later evidence of sensitivity was obtained in about 20 per cent of the subjects. The polymeric form caused no signs of irritation or sensitization. Implantation into mice of the polymeric form did

not cause tumor growth. In this connection it is of interest that Laskin *et al.* (5) have recently found that the subcutaneous implantation of methyl methacrylate film in mice resulted in a 25 per cent incidence of fibrosarcomas (without metastases), while the incidence of fibrosarcomas with cellophane implants was 14 per cent. Contact lenses are made from methyl methacrylate and cause no irritation and are not distorted in shape by any temperature the body can endure. Odors and irritating fumes arise when plexiglas burns and to a lesser extent from sawing the plastic due to the heat of friction. The heavy odor is reminiscent of burnt camphor and the irritation produced is of sufficient degree to provoke immediate coughing and respiratory tract discomforts (6).

### Analysis

The analytical method developed by Deichmann (3) for estimating methyl methacrylate in air is based upon its reaction with potassium permanganate. The methyl methacrylate vapor is passed through absorption towers containing sulfuric acid and a known amount of normal concentration of potassium permanganate. After standing in the dark for 24 hours, a known amount of normal concentration of oxalate is added and the excess oxalate titrated with 0.2000 normal concentration of potassium permanganate. The amount of methyl methacrylate present is read from a graph made by adding known amounts of methyl methacrylate to potassium permanganate and analyzing by the above procedure.

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## METHYL *n*-PROPYL KETONE

### Characteristics

Methyl *n*-propyl ketone, pentanone-2,  $\text{CH}_3\text{COC}_3\text{H}_7$ , is a colorless liquid with an odor resembling that of acetone but more ethereal in character. The boiling point of this ketone is 102.3° C.; the melting point, -77.8° C.; the density,  $d_{20/4}$  0.80639; the index of refraction, 1.39012; and the vapor pressure 30 millimeters of mercury at 20° C.

### Industrial Uses

Methyl propyl ketone is extensively used in industry as a solvent for purposes similar to those for which acetone is employed.

### Toxicity

The acute physiological response of guinea pigs to air containing methyl *n*-propyl ketone (pentanone) was determined by Schrenk and his associates (1), who found that concentrations of 3 to 5 per cent by volume of pentanone were dangerous to life within 30 to 60 minutes, while the maximum amount for several hours of exposure with but slight, or no symptoms, was a concentration of 0.15 volumes per cent. When men were exposed to the latter concentration they noticed a strong odor and complained of marked irritation of the eyes and nasal passages. Pentanone produces narcosis, which terminates in death at higher concentrations. The symptoms noted preceding those of narcosis are principally eye and nasal irritation. Pentanone has a distinct odor and is markedly irritating to man in the higher concentrations, so that it acts as its own warning agent. Specht *et al.* (2) determined the effects of pentanone-2 on guinea pigs over ranges of exposure as long as 510 minutes at a concentration 1.0 volume per cent. He found that this vapor has a very similar action to that of methyl ethyl ketone in depressing such various functions as a rectal temperature, respiration, and heart rate. The average time of onset in animals of irritation, weakness, coma, and death at various concentrations of the gases of these two ketones is nearly alike.



## Analysis

Although it is not specific for methyl *n*-propyl ketone, the iodine titration method may be used for estimating the amount of this ketone in air. Somewhat higher results than the theoretical values are obtained by this method (2), but, properly calibrated, it can be applied to the analysis of air samples containing methyl *n*-propyl ketone as a contaminant.

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## METOL

### Characteristics

Metol, methyl-*p*-aminophenol sulfate,  $\text{elol, (HOC}_6\text{H}_4\text{NHCH}_3)_2\text{H}_2\text{SO}_4$ , forms colorless needle-like crystals which are soluble in 10 parts of cold water and in 3 parts of cold concentrated hydrochloric acid, but are insoluble in alcohol and ether. Photographic metol discolors in air, giving off the odor of methyl isocyanide, and it should be kept in a well-closed container and protected from light. It melts at about 260° C. with decomposition. It is prepared by the methylation of *p*-aminophenol and conversion of the resulting methylated base by neutralization with sulfuric acid.

### Industrial Uses

During the year 1945, 504,000 pounds of metol were manufactured in the United States. Metol alone, or in combination with hydroquinone, has been one of the most popular of all photographic developers since its introduction by Hauff in 1891. It is a rapid, soft-working developer and is only slightly affected by the presence of bromide or other restrainers. Minor uses of metol include developing out papers, lantern slides, and the dyeing of furs.

## Toxicity

Metol used in certain photographic developers causes dermatitis in individuals sensitized to it. The effect of skin contact to metol is first made evident by inflammation and swelling of the afflicted parts, usually the backs of the fingers and back of the hand, and the interdigital spaces. This is followed by the appearance of papules and vesicles which ulcerate either spontaneously or when scratched and which later become covered with crusts. Individuals do not become desensitized and relief is secured only by completely avoiding contact with this substance once sensitization has occurred. Drew (1) describes the dermatitis and points out that the metol crystals cause more damage than the solution, although this is disputed. According to Drew, the rash is caused by a dimethyl impurity rather than the metol itself, excepting in the case of especially sensitive individuals. Once the dermatitis has occurred the skin becomes still more sensitive. Washing in dilute acid, plain water, and then soapy water is suggested as a safeguard. Boström (2) states, too, that pure metol is relatively harmless and that certain impurities, especially the dimethyl derivatives, are poisonous and cause the skin eruptions. Wagner (3) describes the symptoms produced on the skin (usually on the hands and under the arms) of workers who are allergic to metol and points out its similarity to frostbite and eczema. Skin irritation from contact with metol is due to the presence of *n,n*-dimethyl-*p*-phenylenediamine as an impurity according to Greenwood (4). Although occupational poisoning from contact with metol is largely a matter of skin irritation, cases of poisoning from accidental ingestion of metol, with one fatality, have been reported (5, 6). Dinitrophenol used in the manufacture of metol is reduced to basic diaminophenol. Metol itself is prepared by the methylation of this material and workmen may be exposed to the vapors of methyl sulfate which is irritating to the eyes and mucous membranes.

### Analysis

*p*-Methylaminophenol sulfate gives a purple color with ferric chloride in acid solution

in the cold and it gives the odor of quinone when warmed. With benzaldehyde in alkaline solution, no precipitate is formed while with sodium nitrite in acid solution colorless needles (melting point  $136^{\circ}\text{C}$ .), which are slightly soluble in water, are formed (7).

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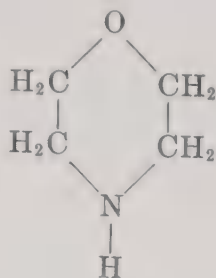
### MORPHOLINE

#### Characteristics

Morpholine, tetrahydro-1,4-oxazine, is a colorless, mobile, hygroscopic, caustic, and alkaline liquid having an ammoniacal, but not unpleasant, odor. It is volatile to some extent at room temperature. It is obtained from 2,2'-iminodiethanol,  $\text{NH}(\text{CH}_2\text{—CH}_2\text{—OH})_2$ , by heating with 70 per cent sulfuric acid at  $160$  to  $170^{\circ}\text{C}$ ., or in better, nearly quantitative, yield from the di-2-naphthyl ether of N-toluenesulfonyl-2,2'-iminodiethanol,



(Meyer, 1). Morpholine is a six-membered ring compound containing two different hetero atoms:



and was so named because for a long time morphine was erroneously assumed to contain a similar ring. Morpholine boils at  $128.9^{\circ}\text{C}$ ., has a density of  $d_{20/4}$  0.9994 and an index of refraction of  $n_{20/D}$  1.4545 (2). It is miscible with water and volatile with steam. However, dilute solutions boil with but little change in composition. A constant alkalinity is maintained both in the solution and its distillate and for this reason morpholine is used to reduce corrosion in closed boiler systems. Pure morpholine has a relatively high vapor pressure of 13 millimeters of mercury at  $20^{\circ}\text{C}$ .

#### Uses

Morpholine has extensive industrial applications (3). It forms soaps with fatty acids which are excellent emulsifying agents for use in paper coatings and nonrubbing floor polishes. It is notable for its solvent power for waxes, resins, dyes, and casein and has been used to prevent the tarnishing of silver (4).

#### Toxicity

The physiological response to morpholine was investigated in an extensive study by Shea (5). In that study it was found that daily dosing by mouth and skin application of 0.08 gram of free base per kilogram of body weight resulted in death or permanent damage of white rats, providing this amount of morpholine was actually absorbed. The MLD of diluted morpholine was found to be 1.6 grams per kilogram of weight for white rats. Lung damage from inhalation of the vapor was characterized by the similar effects from ammonia. Liver damage in this case was found to be more extensive than after administration by mouth. Neutralized morpholine is not absorbed through the skin. Shea noted no evidence of cumulative or chronic effects from exposure to morpholine. It was found that a concentration of 12,000 parts per million was irritating to humans and probably is intolerable for long periods of time. This is a much higher concentration than that of ammonia gas of 2,500 to 6,500 parts per million, which is dangerous for even short exposures of  $\frac{1}{2}$ -hour duration (6). Smyth *et al.* (7) report the single dose



toxicity of morpholine for rats ( $LD_{50}$  after 14 days) to be 1.05 grams per kilogram. The inhalation of 8,000 parts per million for 8 hours resulted in a mortality of only 1/6 in 14 days. It may be concluded therefore that morpholine has a relatively low toxicity rating and that no extraordinarily great precaution is required in handling this substance. However, it is suggested that extensive, or continuous, skin contact should be avoided.

### Analysis

According to Malowan (8), Nessler's solution precipitates fine, white crystals consisting of mercuric iodide in loose combination with several molecules of morpholine when added to this substance. Shupe (9) states that extracted morpholine can be quantitatively titrated with standard acids, using methyl red as an indicator. Shupe also cites a variety of qualitative tests for morpholine.

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### NAPHTHA

The numerous substances comprising the generic term naphtha show such diversity of chemical nature as benzene, toluene, xylene, and cumene on the one hand, and butane, the pentanes, and hexanes on the other. A variety of these naphthas are found in

commerce, characterized by such terms as coal tar naphtha, petroleum naphtha, high flash naphtha, solvent naphtha, and heavy naphtha. While the commercial naphthas have definite specifications with reference to percentage of constituents, boiling points, and specific gravities, characterization in the chemical sense is not possible since they merely represent several mixtures of various constituents.

During 1953, solvent naphtha produced from coke-oven operation was 6,285,346 gallons (1, 2). Distinction must be made, between coal tar naphtha and petroleum naphtha from the point of view of toxicity. The petroleum naphthas, in general, are less dangerous to animal life than the coal tar naphthas, since the latter contain well-known definitely toxic constituents, while the petroleum naphthas contain constituents which are far more toxicologically inert. The term "gasoline" originally was synonymous with the product known as petroleum ether, which has a relatively low boiling point ranging from 20° to 60° C. and consists largely of butane, the pentanes, and hexanes. However, commercial gasoline has changed in composition with time and may contain very little of the constituents originally found in this product. Stoddard Solvent is a petroleum distillate widely used as a dry-cleaning agent. It has definite specifications for distillation range, flash point, and acidity.

Ordinary gasoline vapor is by no means harmless and men employed in restricted quarters where gasoline fumes are heavy, such as in cleaning the interior of storage tanks or tank cars which have contained gasoline, are likely to be overcome by the inhalation of vapor of this type. Cases of intoxication of men from gasoline fumes have been reported from time to time (3, 4) and two fatal cases of this type have been reported by Dixon and Pardo (5). However, Amorati and his associates (6) found no evidence of chronic poisoning in workers exposed over long periods of time to the vapor of pure gasoline. Individuals exposed to coal tar naphtha are not only likely to exhibit the symptoms of dizziness and narcosis which characterize ordinary gasoline but may suffer from chronic poisoning due to

aromatic substances, such as benzene or its homologues. According to Henderson and Haggard (7), the maximum concentration allowable for prolonged exposure to gasoline is 1,000 to 1,500 parts per million.

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### NAPHTHALENE

#### Characteristics

Naphthalene, tar camphor,  $C_{10}H_8$ ,



is a white crystalline solid which is contained in large quantities in coal tar. It has a characteristic aromatic odor, melts at  $80.1^\circ C$ , boils at  $217.9^\circ C$ , is volatile to a certain extent at room temperature, and is freely volatile in steam. It is insoluble in water but is appreciably soluble in benzene, alcohol, and ether, and in certain fixed and volatile oils. The aromatic character of naphthalene is shown in the ease with which it may be sulfonated, chlorinated, and nitrated. The reduction of naphthalene with hydrogen has become commercially important and is carried out with hydrogen and finely divided nickel in autoclaves at high temperatures. Very pure naphthalene from which all catalyst poisons have been removed is required for this process. These products, one of which with four additional hydrogen atoms is tetrahydronaphthalene (tetralin),  $C_{10}H_{12}$ ,

and another with ten additional atoms is decahydronaphthalene (decalin),  $C_{10}H_{18}$ , are used commercially as solvents for waxes, resins, rubber, gums, and a variety of other commercial substances. Naphthalene forms molecular compounds with such nitrocompounds as trinitrobenzene and trinitrotoluene which have definite melting points. With picric acid, it forms naphthalene picrate which crystallizes into long, hairlike, yellow crystals melting at  $150.5^\circ C$ .

#### Industrial Uses

The production of naphthalene in the United States in 1954 amounted to 71,151,000 pounds. The greater part of the naphthalene consumed is used for the production of phthalic anhydride (about 65 per cent). Other intermediates account for about 20 per cent, while repellents and insecticides account for less than 10 per cent. In the form of "moth balls", naphthalene has been in household use for many years.

#### Toxicity

The toxicity of naphthalene is rather low even on ingestion since it is absorbed only to a small extent, the greater part being eliminated unchanged in the feces. Naphthalene has been employed in fact as an anthelmintic in doses as great as 0.2 gram three times daily. Exposure to the vapor of naphthalene is not great under ordinary conditions since the vapor pressure is relatively low (0.10 millimeter of mercury at  $25^\circ C$ ). It has been stated, however, that continued inhalation of the vapor even from residual naphthalene on bedclothes may cause such toxic symptoms as malaise, headache, and vomiting (1). Most cases of poisoning which have been reported refer to children who have eaten moth balls (2, 3). Naphthalene cataracts have been reported in laboratory animals following the administration of naphthalene by stomach tube. The inhalation of naphthalene vapor in cases where this substance has been vaporized in oil for medicinal purpose has been reported to cause nausea, vomiting, headache, hematuria, and occasional damage to the cornea, retina, and lens. Skin reaction to naphthalene is rare (4). No serious industrial cases of injury



from inhalation of naphthalene vapor, nor of the vapors of tetralin or decalin, have been reported and no maximum allowable concentration value has been established for these substances.

### Analysis

No very satisfactory specific method has been developed for the sampling and analysis of air containing naphthalene vapor as a contaminant where the latter exists in minute amount. When naphthalene vapor is present in quantity, the picric acid method may be applied to the analysis of the sample. Dobrovolskaya (5) has developed a method in which the air is passed through a nitrating mixture and later, after this absorbing mixture is poured into water, the deposited trinitronaphthalene is dissolved in ether. This residue dissolved in water is compared in a colorimeter with a dilute methyl red solution which had previously been standardized against trinitronaphthalene. With appreciable amounts of naphthalene, even in the presence of tetralin and decalin, the cloud point temperature method of Cervený and his associates (6) may be applied. Identification of decahydronaphthalene may be made by its conversion to the mononitro derivative and subsequent reduction to the amine. Tetrahydronaphthalene yields phthalic acid on oxidation (melting point  $195^{\circ}\text{C}$ .) and on bromination at  $100^{\circ}\text{C}$ . yields a dibromoderivative (melting point  $70^{\circ}\text{C}$ .). Naphthalene develops a green color on adding dry aluminum chloride to its solution in chloroform. With *m*-dinitrobenzene dissolved in benzene, naphthalene forms a dinitrobenzene derivative melting at  $52^{\circ}\text{C}$ .

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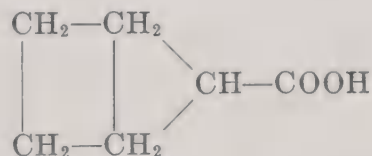
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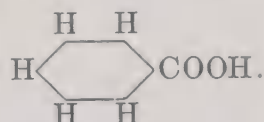
## NAPHTHENIC ACID

### Characteristics

The term "naphthenic acid" is applied to a mixture of carbocyclic acids obtained from crude petroleum. They were first found in the naphthene-containing oils from Russia and Roumania, which are particularly rich in acidic constituents. Many of them have the general formula  $\text{C}_n\text{H}_{2n-1}\cdot\text{COOH}$ . The acids up to about  $\text{C}_8$  appear to be aliphatic in character, those from  $\text{C}_8$  to  $\text{C}_{12}$  are monocyclic and from  $\text{C}_{12}$  to  $\text{C}_{23}$  are bicyclic. While the ring structure in many of the naphthenic acids is that of a cyclopentane with a carbonyl group at the end of an alkyl side chain, as typified by cyclopentane monocarboxylic acid,



"ordinary" naphthenic acid, hexahydrobenzoic acid is cyclohexanecarboxylic acid



The acids are obtained by agitating crude oil with sodium hydroxide solution. The water-soluble sodium salts are then decomposed with mineral acids. Naphthenic acids of Russian origin are more or less dark, low-boiling liquids, often with a foul odor; those from American oils are said to be nearly odorless. Oils poor in paraffin are relatively rich in naphthenic acids, while the reverse is true of oils rich in paraffin. They vary in physical character from colorless or colored liquids sparingly soluble in water to crystalline solids. Since they exist more or less as mixtures, their physical and chemical characteristics are relatively unimportant.

### Uses

Naphthenic acids have many applications in industry. The sodium salts are important detergents and emulsifying agents, while the calcium and barium salts are used in the preparation of colored lakes for printing inks. They are also used for such diverse purposes as the regeneration of vulcanized rubber, as a constituent of fungicides, as metallic salts in paint driers, and in synthetic resins and lacquers. The commercial importance of these acids is reflected in the production figures for the United States of 23,654,000 pounds in 1949, with a further import figure of 1,639,019 gallons for that same year. The total production of naphthenic acid salts in this country for 1954 was 19,358,000 pounds.

The naphthenates form a convenient means of introducing a metal radicle in oil-soluble form, and this accounts for the extensive use of copper, manganese, cobalt, lead, and other metal naphthenate salts in the paint industry as driers. Copper naphthenate is extensively used as a wood preservative and is said to be used for the impregnation of sand bags to keep them from rotting. A recently completed 6-year study of the use of copper naphthenate as a wood preservative in the tropics indicated very effective protection against termites and fungi.

### Toxicity

The paucity of information available regarding physiological response to naphthenic acids in general and their possible toxicity is somewhat surprising in view of their industrial importance. While the question of the toxicity of the naphthenates has frequently arisen, the toxic action of the heavy metallic salts is largely attributable to the metal itself. Rockhold (1) has recently shown the naphthenic acids to be slightly toxic when administered orally to rats. The acid derived from crude kerosene acids was found to be approximately one and one-half times more toxic to rats via the oral route than the acid derived from crude mixed acids. No studies have been reported indicating any particular carcino-

genic properties attributable to the naphthenic acids.

### Analysis

While the separation of naphthenic acids from unsaponifiable material may be technically difficult, the determination of the naphthenic acid content itself is merely a matter of titration of its alcoholic solution using phenolphthalein as indicator, as in the determination of fatty acids. Special methods of analysis of naphthenes and naphthenic acids have been reported by Beychok (2) and by Rampton (3).

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## NAPHTHYLAMINE

### Characteristics

Naphthalene resembles benzene in forming nitro, amino, and sulfonic acid derivatives. Two isomeric mono-aminonaphthalenes or naphthylamines,  $C_{10}H_7NH_2$ , the  $\alpha$  and  $\beta$ , are formed.  $\alpha$ -Naphthylamine is a colorless crystalline solid melting at  $50^\circ C.$ , boiling at  $301^\circ C.$ , and having a density of 1.223 at  $25^\circ C.$  It is soluble in alcohol and ether and slightly soluble in water. It has an unpleasant odor, turns red on exposure to air, and gives a blue precipitate with ferric chloride.  $\beta$ -Naphthylamine forms colorless leaflets melting at  $111^\circ C.$ , boiling at  $306^\circ C.$ , and having a density of 1.0614 at  $98^\circ C.$  It is soluble in water, alcohol, or ether, has no odor, and gives no precipitate with ferric chloride. The  $\alpha$  compound is obtained by the reduction of  $\alpha$ -nitronaphthalene with iron and hydrochloric acid after which it is mixed with milk of lime and distilled. The  $\beta$ -naphthylamine is obtained by heating  $\beta$ -naphthol



with aqueous ammonium sulfite or bisulfite (Bucherer reaction, 1904).

### Industrial Uses

The naphthylamines,  $\alpha$  and  $\beta$ , are extensively used in the manufacture of dyes. With mineral acids, both compounds form well-crystallized stable salts. When  $\alpha$ -naphthylamine is hydrolyzed with sulfuric acid under pressure,  $\alpha$ -naphthol is produced with a yield of 94 to 95 per cent. Advantage is taken of these reactions for the preparation of important naphthylamine sulfonic acids and as coupling components in the synthesis of azo-dyes.

### Toxicity

The manufacture of aniline dyes involves the use and production of many chemical substances, and workers employed in the manufacture of synthetic dyes sometimes have been said to suffer from papillomatosis of the bladder. This may eventually become malignant. It was some time before it was found that the responsible chemical was an amino and not a nitro compound. In 1938, Hueper, Wiley, and Wolfe (1) succeeded in producing papillomas and carcinomas in 13 out of 16 dogs treated for a period of 20 to 26 months with subcutaneous injections and oral feeding of  $\beta$ -naphthylamine. They found that prolonged administration of relatively large doses produced blood destruction, degenerative changes in the tubular epithelium of the kidneys and in the parenchyma of the liver. Bonser (2), by massive administration (100 to 700 milligrams per day) of pure  $\beta$ -naphthylamine over a period of 5 years, produced a series of change in the bladder epithelium of the dog, ranging from simple hyperplasia to anaplastic carcinoma. The renal pelvis, ureters, and urethra were free from tumors. The bladder tumors only develop after a long latent period (usually 10 to 25 years in man) and sometimes not until many years after the men have ceased work. Goldblatt (3) finds there is a greater incidence of bladder cancer in occupations involving exposure of employees to coal gas, tar, pitch, and soot than occurs in the general population. The highest incidence of this disease is in the manufacture of organic

intermediates, in which  $\beta$ -naphthylamine and benzidine are known factors and aniline and  $\alpha$ -naphthylamine are possible factors. Other compounds cause methemoglobinuria and hemorrhagic cystitis but these do not give rise to bladder cancer. As to the route of absorption, Hunter suggests that the respiratory tract, as well as the skin, may be involved, for occasionally members of the clerical staff of dye industries have developed bladder tumors. A number of men may work together in a dye factory for 30 years under apparently identical conditions and, although bladder tumors may arise early in some and late in others, the majority remain unaffected (4). Workers should be warned concerning the risk of working with this substance and should be informed of early symptoms which are those of cystitis, such as frequency of urination with strangury and the hematuria which may occur later.

### Analysis

$\alpha$ -Naphthylamine forms colored precipitates with cadmium, cobalt, gold, iron, manganese, and mercury ions. In an acetic acid medium, a mixture of  $\alpha$ -naphthylamine and sulfanilic acid reacts with nitrous acid, giving a soluble red compound.  $\beta$ -Naphthylamine hydrochloride yields colored precipitates with the above metallic salts. *p*-Methoxyphenyl-*iso*-thiocyanate has been proposed as a method of identifying these amines, the  $\alpha$ -naphthylamine derivative melting at 162 to 163° C., and the  $\beta$ -naphthylamine derivative at 160° C. (5). Since  $\alpha$ -naphthylamine couples with sodium benzenesulfonate-*p*-diazonium chloride, this may be made the basis for its colorimetric estimation (6).  $\beta$ -Naphthylamine in the presence of calcium hypochlorite produces a yellow color in acid solution which is useful in determining it colorimetrically (7).

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## **$\alpha$ -NAPHTHYLTHIOUREA**

### **Characteristics**

$\alpha$ -naphthylthiourea,  $\alpha$ -naphthylthiocarbamide, *n*-1-naphthylthiourea, 1-(1-naphthyl)-2-thiourea,  $C_{10}H_7 \cdot NH \cdot CS \cdot NH_2$ , also commonly called Antu, is a very stable, white, crystalline solid having a melting point of 184° C. It is prepared by warming an aqueous solution of  $\alpha$ -naphthylamine with ammonium thiocyanate acidified with hydrochloric acid. It is also prepared by treating  $\alpha$ -naphthylisothiocyanate with alcoholic ammonia. Because of its stability it does not deteriorate on standing and, owing to its high melting point, it is unaffected by temperatures well above those ordinarily encountered in use. Its solubility in most liquids, such as ether and cold alcohol, is low and in water it dissolves to the extent only of a few milligrams per 100 milliliters. It is, however, rather soluble in boiling alcohol from which it may be crystallized.

### **Toxicity**

The peculiar property that  $\alpha$ -naphthylthiourea exhibits of being nearly a specific poison for the control of Norway rats, while having a low toxicity to a number of other species of animals, was discovered by Richter (1). In the course of an investigation concerning an unrelated problem on taste threshold, Richter (2) found that phenylthiocarbamide was especially toxic to rats. Further investigation of analagous substances revealed  $\alpha$ -naphthylthiourea to be an excellent rodenticide. Subsequent investigation by McClosky and Smith (3) and by Lillie (4) showed that the acute

toxicity of Antu varies with different species of animals—rats and dogs being the most susceptible. Furthermore, a certain tolerance to the acute toxic action of Antu can be induced in rats by administering progressive doses, while chronic toxicity experiments with rabbits and cats indicate an accumulative effect. Lillie found that Antu produces a fatty degeneration of the liver of fine-droplet type in rats, rabbits and cats. Pulmonary edema was noted in rabbits and cats and a moderate splenic and hepatic hemosiderosis was found in cats and splenic hemosiderosis in rabbits following the administration of Antu. According to DuBois and his associates (5),  $\alpha$ -naphthylthiourea produces intense pulmonary edema in rats. Byerrum (6) found that iodine, whether administered as Lugol's solution or as potassium iodide, protects rats against  $\alpha$ -naphthylthiourea. According to Fitzhugh and Nelson (7) the degree of injury to rats following oral administration is related to the concentration of  $\alpha$ -naphthylthiourea. Brion (8) found that the average lethal dose for wild rats is 10 milligrams per kilogram of body weight, while for domestic animals it is 100 to 200 milligrams per kilogram for cats and pigs, 500 milligrams per kilogram for dogs and 1,000 milligrams per kilogram for chickens.

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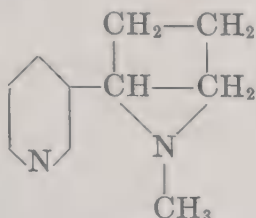


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## NICOTINE

### Characteristics

Nicotine,  $\beta$ -pyridyl- $\alpha$ -N-methylpyrrolidine, 1-methyl-2(3-pyridyl)pyrrolidine, having the structure



is a colorless to yellowish, oily liquid which gradually becomes brown on exposure to air. The pure, colorless oil boils at  $246.1^{\circ}\text{C}$ . at 230.5 millimeters, has a density of  $D_{20/4} 1.00925$  and an index of refraction  $n_{20/D} 1.5286$ . Nicotine freezes at about  $-79^{\circ}\text{C}$ . It is laevrorotary ( $\alpha_{20/D} -167$ ), and has a vapor pressure of 0.0425 millimeters of mercury at  $25^{\circ}\text{C}$ . It distils unchanged in steam, is miscible with water below  $60^{\circ}\text{C}$ . and is readily soluble in alcohol, ether, petroleum naphtha, and chloroform. Nicotine is the principal poisonous constituent of the tobacco plant. Commercially nicotine is extracted from the ordinary tobacco of commerce (leaf stems and tobacco refuse) *Nicotiana tabacum* L. and to some extent from a coarser tobacco, *Nicotiana rustica* L. The latter is said to have a higher content of the alkaloid. Nicotine is one of about 12 other alkaloids found in the tobacco plant and occurs to the extent of about 4 per cent in the dry leaf. As a rule it does not exceed 6 per cent, although Algerian leaf has been reported as having a nicotine content of 8.9 per cent. It is found in the tobacco leaf as a salt in combination with malic and citric acids. Nicotine is commercially produced by treating tobacco stems and other tobacco refuse with alkali followed by steam distillation. It is usually marketed in the form of the sulfate in 40 per cent solution. While the base itself is laevrorotary, the salts are dextrorotary. The salts are water-soluble and

crystallize readily. Several methods for the synthesis of nicotine have been evolved since A. Pictet originally synthesized this substance. The synthetic product is d,1-nicotine. This can be resolved into its enantiomorphous forms by means of the tartrate.

### Uses

The export of nicotine sulfate from this country amounted to 1,054,000 pounds during the first 10 months of 1949 (1) and the annual production is stated to be more than 5,000,000 pounds (2). Nicotine sulfate is chiefly used as an insecticide and is particularly useful as a contact poison. It is applied as a spray either directly or as a bentonite mixture. Finely ground tobacco is applied as a dust in many instances, while dusts carrying nicotine sulfate, such as talc, kaolin, fuller's earth, gypsum, and hydrated lime, are widely used. Nicotine is especially useful against the green fly (Aphides) and the white fly (Aleurodes), but has limited application against caterpillars. It is also used in a  $1\frac{1}{2}$  to 2 per cent solution as a dip for the destruction of the itch-mite of sheep and to destroy the itch-mite ova.

### Toxicity

The present discussion is solely concerned with poisoning from the alkaloid nicotine and does not refer to the use of tobacco. The literature of nicotine poisoning is replete with cases of fatal or near-fatal effects arising from ingestion or skin contact with this substance. These cases include its administration with criminal intent, as in the famous case of Count Bocarmé, numerous cases of suicide, cases where nicotine solutions have been mistaken for innocuous material, or where nicotine solution has been spilled on the skin. According to the Mortality Analysis Branch, Vital Statistics, U. S. Public Health Service, there were 487 cases of fatal poisoning from nicotine in the United States from 1934 to 1950, of which 307 were suicidal. The extensive production of nicotine sulfate and its wide application as an insecticide emphasize the need for more lively appreciation of the marked toxicity of this substance.

The rapidity and fatality of poisoning with nicotine approach that of hydrogen cyanide. Death usually occurs within a few minutes, or even seconds, following the administration of a large dose. The symptoms displayed are those of paralysis of the central nervous system, including the respiratory center. Smaller quantities cause salivation, nausea, vomiting and sometimes purging. The breathing is labored, the pulse very irregular; mental confusion, muscular weakness, giddiness, and lack of coordination are marked and may be followed by partial or complete unconsciousness. Clonic convulsions may occur, followed by collapse with muscular relaxation, slow and weak respiration which finally ceases, although the heart may continue to beat for some time following respiratory failure. The natural laevo form of nicotine is stated to be two or three times as poisonous as the synthetic dextro form.

The distressing effects of minute amounts of nicotine are familiar to most novices at smoking. The metabolism of nicotine is still imperfectly understood. According to Werle (3) the lung, liver, and kidney of the rabbit effect a detoxicating action due to an enzyme. The liver was found to be outstanding in its detoxicating action which is apparently dependent upon the presence of oxygen.

Only part of the total amount of nicotine administered is excreted. Haag and Larson (4) found that small doses of the order of 0.2 milligram per kilogram of nicotine when injected subcutaneously in dogs appear to the extent of about 10 per cent unchanged in the urine while the remainder is found in the nicotinic fraction. However, although there was an increase in this fraction, this increase was found to be not due to nicotinic acid, nor to nicotinuric acid, nicotinamide, trigonelline or 1-methyl pyridinium hydroxide in measurable quantities. The fate of nicotine in the body is naturally of great interest because of the extent of exposure of human beings to small amounts as a result of smoking. In cases of nicotine poisoning medical treatment should be prompt. It has been recommended that gastric lavage with activated charcoal which adsorbs the al-

kaloid, or with tannic acid which precipitates it, should be accompanied by artificial respiration, if needed, including the inhalation of oxygen. Where nicotine solutions have been spilled on the skin washing should be prompt and thorough. Davies (5) states that only cold water should be used for washing the skin, since warm water causes vasodilation and thus increases absorption.

### Analysis

Since exposure to nicotine may occur in the manufacture, handling or application of this substance, detection and determination of the atmospheric concentration, where it may be present as mist or in dust, may be of occasional importance. Nicotine responds to most of the usual precipitation tests for alkaloids and also gives several color reactions (6). It may be sampled by drawing air through bubblers containing dilute sulfuric acid. Quantitative estimation may be made by reduction of the compound formed by precipitation with silicomolybdic acid (7) and comparison of the blue color thus formed with that of nicotine standards. One part in 40,000 may be detected by this means and may be quantitatively estimated with an accuracy within 2 or 3 per cent. The colorimetric method recently developed by Fabre and his associates (8) is accurate over the range of 0 to 100 micrograms and is particularly applicable to air analysis and the determination of minute amounts of nicotine in biological material.

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## NITROBENZENE

### Characteristics

Nitrobenzene,  $C_6H_5NO_2$ , is a colorless to faintly yellow, oily, hygroscopic liquid. It is not miscible with water, is volatile with steam, is soluble in alcohol and ether, and has a remarkable solvent power for organic compounds. It boils at  $210.85^\circ C$ ., melts at  $5.7^\circ C$ ., and has a density of 1.198. It has a characteristic sweetish odor and is sometimes called "oil of mirbane" or artificial oil of bitter almonds. In the formation of nitrobenzene, the introduction of the first nitro group into the benzene nucleus is readily accomplished by means of nitric acid. On a technical scale, yields up to 98 per cent are accomplished by nitration of benzene with concentrated nitric acid and concentrated sulfuric acid at  $50$  to  $55^\circ C$ . The sulfuric acid removes the water produced and accelerates the reaction.

### Industrial Uses

Nitrobenzene is used in the manufacture of aniline, aniline dye intermediates and explosives, as a perfume for scenting soap, and as an oxidizing agent in the manufacture of chemicals. It is employed as a crystallizing solvent for substances that are practically insoluble in other solvents and since it also dissolves anhydrous aluminum chloride as a result of the formation of a complex compound, it is a useful solvent for the Friedel and Crafts reaction. It is used in shoe dyes, inks, polishes, glues, greases, and cements. During 1954, 122,548,000 pounds of nitrobenzene were produced in the United States.

### Toxicity

Nitrobenzene is decidedly toxic (1). Because of the wide range of use of substances containing nitrobenzene, poisoning with this agent is probably more common than is generally believed, although most cases are mild (2). In fatal cases, the major autopsy find-

ings are marked cyanosis, marked congestion, and, in moderate number, multiple subserous hemorrhages. In these cases, the nitrobenzene is found in liver, brain, stomach, and blood. In a fatal case reported by Chambers and O'Neill (3), the blood was chocolate-brown in color and microscopic examination revealed intracellular and extracellular deposits of small granules of dark brown pigment.

Industrially, skin absorption is the most likely source of poisoning, though entrance through the respiratory or digestive tracts may also occur. Skin absorption occurs from the wearing of clothes badly soiled by splashing of nitrobenzene or from lack of cleanliness of the workman. Subacute and chronic forms of poisoning may follow repeated absorption of small doses of nitrobenzene. Anemia is the leading feature of the clinical picture, although fatigue, vertigo, headache, loss of appetite, vomiting, general weakness, and numbness of the legs also occur. Nitrobenzene is more poisonous to the nervous system than is dinitrobenzene. The inhalation of high concentrations is followed by intoxication, extreme cyanosis, coma, and death. The hemoglobin of the blood is converted into methemoglobin. Polychromatophilia, punctate basophilia, anisocytosis, and poikilocytosis are found and, where the anemia is severe, normoblasts are present. Even the moderate drinking of alcohol aggravates the toxic effects of nitrobenzene and workers should be informed of this danger. Henderson and Haggard (4) report that 200 parts per million is the maximum concentration that can be inhaled for 1 hour without serious disturbance and that 1 to 5 parts per million are considered safe for daily exposure.

### Analysis

For the determination of small amounts of nitrobenzene in air, Strafford and Harper (5) have developed the following method: Air is sucked by hand pump through filter paper impregnated with absorbent carbon. The absorbed nitrobenzene is then determined by reduction to aniline by titanous sulfate, separation of the aniline by steam distillation, and determination in the dis-

tillate by means of the color developed by diazotization and coupling with R salt. It is claimed that the method is sensitive from 0.2 to 100 parts per million.

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## NITRO DERIVATIVES OF ANILINE

### Characteristics

With the introduction of one nitro group into the aniline ring,  $\text{NO}_2\text{C}_6\text{H}_4\text{NH}_2$ , *o*-, *m*-, and/or *p*-nitroaniline are formed. *o*-Nitroaniline forms orange-yellow rhombic crystals of specific gravity 1.442 at 15° C. and melting point 71° C. Its solubility in water at 25° C. is 1.25 grams per liter of solution and it dissolves to the extent of 278.7 grams per liter of alcohol. *m*-Nitroaniline forms yellow rhombic crystals of specific gravity 1.388 at 18° C., melting point 114° C., and boiling point above 285° C. *m*-Nitroaniline dissolves to the extent of 1.205 grams per liter of solution at 24.2° C. and in alcohol, to the extent of 77.78 grams per liter at 25° C. *p*-Nitroaniline forms yellow monoclinic crystals of specific gravity 1.437 at 14° C. and melting point 147° C. It dissolves to the extent of 0.77 gram per liter of aqueous solution at 20° C. and in alcohol, to the extent of 60.48 grams at 25° C. per liter of this solvent.

When aniline is treated with concentrated nitric acid, nitration and oxidation usually both occur. When the nitroamine is to be obtained, the amino group must be protected and this is done by acetylating it or carrying out the nitration in concentrated sulfuric acid. The position the nitro group takes with respect to the amino group depends on the method used. Nitration in concentrated sul-

furic acid produces approximately equal quantities of the *m* and *p* derivatives. The *o* and *p* derivatives may be obtained by heating the corresponding nitrochlorobenzenes with ammonia. The basic properties of aniline are diminished by nitro groups in the *o* and *p* position, while *m*-nitroaniline is but slightly weaker as a base than aniline. The varying basic properties of the nitroanilines can be used as a means of separating them. The *o*- and *p*-nitroanilines differ from aniline in their reactivity with alkalies with the displacement of the amino group by a hydroxyl group.

### Industrial Uses

*o*-Nitroaniline has no commercial uses. It is, however, useful as a laboratory agent for the detection of iodides and has a high degree of sensitivity for this test. The *m* derivative is used for the preparation of azo dyes and for *m*-phenylenediamine. It is used in the laboratory as a reagent for identifying pine wood. *p*-Nitroaniline is the starting substance for the preparation of dyes and explosives. Specifically, it is used for the production of *p*-nitroaniline red and for *p*-phenylenediamine. It is used in the laboratory as a reagent for the detection of ammonia.

### Toxicity

The nitroanilines are active skin poisons and when sufficiently volatile are dangerous, if inhaled. According to Hunter (1), *p*-nitroaniline is more toxic than aniline itself and *m*-nitroaniline is more poisonous than *p*-nitroaniline. The symptoms of acute *p*-nitroaniline poisoning, according to Anderson (2), begin with headache, flushing of face, restriction of breathing, and occasional nausea and vomiting. There is generalized muscular weakness, somnolence, irritability, and an intense violet-colored cyanosis. The pulse is rapid and thready, the respiration rate is raised. Methemoglobinemia is the essential pathological change. Anderson reported the occurrence of *p*-nitroaniline poisoning with one death in Persian dock laborers handling the dye in powder form where the hot, moist weather conditions assisted the absorption of the toxic substance. The intravenous injection of a concentrated solution of methyl-



ene blue brought about rapid relief of symptoms in three patients to whom it was administered. Gupta (3) has also reported several cases of acute nitroaniline poisoning in dock workers sweeping up spilled nitroaniline in the hold of a ship. All the men recovered rapidly.

Removal from contact, removal of contaminated clothing, bathing the patient, and rest are most important in the treatment of acute *p*-nitroaniline poisoning. Hamblin and Mangelsdorff (4) showed that methemoglobinemia is an index of the severity of the clinical picture in *p*-nitroaniline poisoning and that the latter increased in direct proportion to a rising concentration of methemoglobin and decreased with a falling concentration. Brieger and his associates (5, 6) have traced the poisoning of children eating wax crayons colored with para red to an impurity of unreacted *p*-nitroaniline in the coloring material. Recovering from *p*-nitroaniline poisoning is stated to be slower than recovery from aniline poisoning. It is suggested that the maximum allowable concentration value for any of the nitroanilines should be less than the accepted value of 5 parts per million of aniline, since the former are more toxic than aniline itself.

### Analysis

*o*-Nitroaniline and *m*-nitroaniline may be determined by absorption in hydrochloric acid solution, bromination with an excess of bromide and potassium bromate reagent, and the excess estimated by the use of potassium iodide and standard thiosulfate solution. The titanous chloride method may be used to estimate *p*- and *m*-nitroaniline. *m*-Nitroaniline may be detected by the brownish color developed with 1,2-naphthoquinone-4-sulfonic acid in alkaline solution.

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## NITROETHANE

### Characteristics

Nitroethane,  $C_2H_5NO_2$ , is an oily liquid having a pleasant odor on initial inhalation. It boils at  $114.8^\circ C.$ , melts at about  $-50^\circ C.$ , has a density  $D_{20/20}$  of 1.052, an index of refraction  $n_{D20}$  of 1.392, a vapor pressure of 15.6 millimeters of mercury at  $20^\circ C.$ , and a flash point of  $27.7^\circ C.$  Nitroethane is somewhat soluble in water, 45 milliliters dissolving in 1 liter of water at  $20^\circ C.$  Unlike the aromatic hydrocarbons, the hydrogen of the paraffin series is not readily replaced by the nitro group and the method of preparation of the nitroparaffins for many years consisted in heating the iodides of the alcohol radicals, such as ethyl iodide,  $C_2H_5I$ , with silver nitrite. The comparatively recent vapor phase nitration method of Haas (1936) has made the production of such substances as nitroethane commercially possible. In this process a gaseous mixture of 2 mols of hydrocarbon and 1 of nitric acid vapor is passed through a narrow reactor tube at  $420^\circ C.$  Ethane reacts rapidly and the unacted upon hydrocarbon is recycled to near completion. It is then purified from degradation products. The nitroparaffins are important substances from the point of view of synthetic chemistry and the structure of the nitro group differs from that of the nitro group of the aromatic nitro compounds, as has been shown by comparative refractometric investigation of nitroethane and nitrobenzene.

### Industrial Uses

Nitroethane is a solvent for such substances as nitrocellulose, cellulose acetopropionate, cellulose acetate, and cellulose acetobutyrate. In addition, it is an excellent solvent for vinyl, alkyd, and other resins, as well as certain fats and waxes. The nitroparaffins are used as the starting point for the synthesis of a number of substances in

the chemical industry and for the preparation of related products and derivatives, such as chloronitroparaffins, nitroalcohols, and aminoalcohols.

### Toxicity

Machle and his associates (1) have made an extensive investigation of the physiological response to the nitroparaffins in general, including nitroethane. A concentration of 0.05 per cent by volume of the vapor of nitroethane was found to be a safe and tolerable concentration for guinea pigs, rabbits, and monkeys. Nitroethane is slightly irritating on continued inhalation and since the odor of the material is definitely disagreeable to most observers, it constitutes its own warning agent. No evidence of significant skin absorption of nitroethane was found by these observers. Further investigation by the above investigators (2) and by Scott (3) on the metabolism of nitroethane indicates that following the intravenous injection of rabbits, nitroethane is partially excreted by the lungs, and after a dose of 1 gram given by this route the amount that can be recovered from tissues of animals gradually decreases in 30 hours to almost nil. Apparently oxidation of this material occurs since both acetaldehyde and nitrite were found in relatively large amounts in the blood of rabbits following such injections.

### Analysis

The absorption curve of the colored complex formed when ferric chloride is added to nitroethane, previously acidified with hydrochloric acid to a pH of 1.25–1.30, is the basis of the quantitative determination of nitroethane as devised by Scott and Treon (4).

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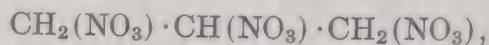
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termination of primary mononitroparaffins. *Ind. Eng. Chem., Anal. Ed.* 12: 189 (1940).

## NITROGLYCERIN

### Characteristics

Nitroglycerin, glyceryl trinitrate,



is a nitric acid ester of glycerol. It is a colorless, oily liquid with a sweet, burning taste and is only very slightly soluble in water, although it dissolves freely in alcohol or ether. It is produced by the action of a mixture of sulfuric and nitric acids on glycerol. It crystallizes in two forms, one of which is labile and melts at 2.9° C. and the other is stable, melting at 13.2° C. Its density is about 1.6. The most significant property of nitroglycerin is its sensitiveness to slight shock which causes violent detonation. Kieselguhr, a diatomaceous earth, will absorb up to two or three times its weight of nitroglycerin and still remain dry. This constitutes the important explosive, dynamite, which also is often made by absorbing nitroglycerin on sawdust or charcoal with the addition of sodium or ammonium nitrate. Blasting gelatine, gelatine dynamite, and gelignite all contain gun cotton gelatinized with nitroglycerin as the basic constituent. Alkalies convert nitroglycerin into glycerol and the corresponding alkali metal nitrate.

### Industrial Uses

Apart from war uses, nitroglycerin, as well as dynamite, blasting powder, and gun cotton, are used extensively as industrial explosives. Nitroglycerin is used in medicine to some extent as a vasodilator.

### Toxicity

The powerful vasodilating properties of nitroglycerin have long been recognized and reduced blood pressure is a well-recognized characteristic of nitroglycerin poisoning. Other symptoms include headache accompanied by excitement, vertigo, fainting, respiratory râles, and cyanosis. Terminally, there is respiratory embarrassment and death from asphyxia due to respiratory pa-



ralysis (1). Severe poisoning from nitroglycerin is often manifested by confusion, pugnaciousness, hallucinations, and maniacal manifestations. Alcoholic drinks precipitate attacks and increase the severity. Chronic poisoning causes digestive troubles, tremors, and neuralgia. The most common complaint is a headache which is noted on commencing work and which soon passes off. A break in the work interrupts this acclimatization and workers frequently resort to the device of moistening their hat-bands with nitroglycerin so as to maintain this effect during absence from their occupation. The administration of caffeine sodium benzoate followed by amphetamine is said to alleviate the symptoms of headache, while amphetamine, together with prostigmine bromide, effectively prevents its reoccurrence (2). Industrial poisoning from nitroglycerin occurs either as the result of inhalation of the fume or from skin contact and it is still a moot point as to which route of entrance is the more important. In addition to its toxic action on absorption through the uninjured skin, nitroglycerin produces eruptions characterized by dryness and rhagades, particularly on the palms and interdigital spaces. A study of the waste from a nitroglycerin plant indicates that except for the intermittent acidity the waste from nitroglycerin manufacture would not cause serious difficulty in the receiving stream (3).

### Analysis

Nitroglycerin may be detected in air samples by application of the sensitive Griess test. After reduction to nitrite by means of zinc dust, the addition of sulfanilic acid and  $\alpha$ -naphthylamine solution causes the formation of an azo dye having a red coloration. Yagoda and Goldman (4) have also developed a quantitative method for the estimation of nitroglycerin as an aerial contaminant. This method is based on the formation of an equivalent amount of nitric acid and the corresponding nitration of *m*-xylenol to 5-nitro-4-hydroxy-1,3-dimethylbenzene, followed by its colorimetric determination.

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## NITROMETHANE

### Characteristics

Nitromethane,  $\text{CH}_3\text{NO}_2$ , is a colorless, nonhygroscopic liquid with a melting point of  $-29^\circ\text{C}$ ., boiling point of  $101.2^\circ\text{C}$ ., density  $D_{20/20}$  of 1.139, and refractive index at  $20^\circ\text{C}$ . of 1.3818 (1). The vapor pressure at  $20^\circ\text{C}$ . is 27.8, the flash point is  $44.4^\circ\text{C}$ ., and its solubility is 9.5 milliliters in 100 milliliters of water. Since nitromethane contains a nitro group, its large-scale industrial application is occasionally questioned from the point of view of safety. The flash points of the four nitroparaffins (nitromethane, nitroethane, 1-nitropropane, and 2-nitropropane) are, however, much higher than those of the common hydrocarbons, ketones, and esters having the same boiling points. Attempts to detonate the pure nitrocarbons with blasting caps have been unsuccessful except for nitromethane, which can be detonated only under very special conditions, and it therefore presents no particular safety problem when the usual precautions are observed. However, the nitroparaffins are weak oxidizing agents, particularly at elevated pressure and temperature, and unexpectedly violent reactions may take place, especially in the presence of readily oxidizable organic matter (2). Sodium and potassium nitromethane explode with great violence when heated and this also occurs when these substances, having been dried in a desiccator, come into contact with traces of water. When

mercuric chloride reacts with sodium nitromethane, fulminate of mercury is produced.

### Industrial Uses

The nitroparaffins, in general, including nitromethane, dissolve a wide variety of synthetic resins and cellulose esters and are used commercially as solvents in the coating industry. In coating material having a zein base (a vegetable protein derived from corn), a small amount of nitromethane decreases the tendency of zein solutions to gel and permits the use of less water in the solvent mixture, thus reducing blushing tendencies. Nitromethane is chlorinated to make chloropicrin which, though ordinarily considered a war gas, is employed in large quantities as a soil larvicide and fumigant. It is of interest that nitromethane dissolves aromatic hydrocarbons but is practically immiscible with either paraffinic or naphthenic hydrocarbons. This substance therefore has been of particular value as a solvent in the refining of petroleum.

### Toxicity

The physiological action of nitromethane has been investigated by Machle and his associates (3) using young, healthy guinea pigs, rabbits, and monkeys as experimental animals. The procedure followed included that of oral administration, skin application, and inhalation of the vapor of nitromethane. Concentrations varying from 0.05 per cent of the vapor with an exposure time of 140 hours to concentrations of 3 per cent with an exposure time of 2 hours were used. Initially, there was slight irritation of the respiratory tract but no coughing, sneezing, or marked conjunctival irritation. With continued exposure, however, animals appeared ill, slightly narcotized, and salivation was apparent. The animals later became weak, ataxic, and incoordinated. Pronounced nervous symptoms appeared following continued exposure to the highest concentrations. Guinea pigs and monkeys were somewhat more susceptible than rabbits to nitromethane. Concentrations of 0.05 per cent of nitromethane vapor in air were found to be safe and tolerable concentrations for guinea pigs, rabbits, and monkeys. The concentra-

tion of 0.1 per cent, however, would appear to be a dangerous concentration for man. No evidence of significant skin absorption of nitromethane was found. Since lethal concentrations for animals appear to be less than narcotic concentrations, beginning narcosis cannot safely be used as a warning of dangerous concentrations. However, the strong odor of nitromethane would seem to be an effective guide to the presence of harmful concentrations.

### Analysis

The method adopted by Machle and his associates (3) for the analysis of nitromethane vapor in air is based upon the color formed by heating nitromethane and vanillin in ammoniacal solution. The procedure followed by these investigators is adequate for nitromethane determinations. However, it was necessary to devise a somewhat different method for mixtures containing other nitroparaffins (4). The latter is based on measurements made from the absorption curve of the colored complex formed when ferric chloride is added to a nitroparaffin previously acidified with hydrochloric acid to a pH of 1.25 to 1.30. In the method adopted by Wilson and Hutchinson (5), the nitromethane is absorbed in 0.2 normal concentration of sulfuric acid and the concentration determined polarographically.

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## NITROPROPANE

### Characteristics

Two nitropropanes are commercially important, 1-nitropropane ( $\text{CH}_3\text{CH}_2\text{CH}_2\text{NO}_2$ )



and 2-nitropropane ( $\text{CH}_3\text{CHNO}_2\text{CH}_3$ ). The properties of the pure substances (1) are given in Table 11.

Because of their higher flash points, the nitropropanes are much less hazardous than hydrocarbon solvents having the same boiling range. Furthermore, the nitropropanes present no particular problem from the standpoint of fire or explosion hazard.

### Industrial Uses

The nitroparaffins are solvents for a wide variety of materials (2). Practically all of the cellulose esters and many of the resins used for coating purposes are easily dissolved by these substances. Mixtures containing nitropropanes, ethyl alcohol, and butyl alcohol are used as solvents for lacquers in which cellulose acetate is used. Before the war, 2-nitropropane was used in vinyl resin solutions for coating beer and fruit juice cans and for many other purposes where a corrosion-resistant finish is desirable. Large amounts of nitroparaffins are now used in vinyl resin solutions to replace rubber as dopes or cements for coating cloth. In the dry-cleaning industry, 2-nitropropane has been used as an ingredient of special spotting fluids because of its excellent solvent properties for a wide variety of stains. In the textile field, 2-nitropropane is an ingredient used for scouring and kier-boiling of cotton fabrics. In paint removers, the addition of 20 to 25 per cent of 2-nitropropane permits the attack of many otherwise resistant synthetic finishes.

### Toxicity

Machle and his associates (3), in an investigation of the physiological response of animals to some simple nitroparaffins, administered both 1- and 2-nitropropane by stomach tube to rabbits. The principal symptoms noted were progressive weakness and collapse, unsteadiness, and incoordination ending in complete ataxia. The lethal dose in grams per kilogram of body weight ranged between 0.25 and 0.50 for 1-nitropropane and between 0.50 and 0.75 for 2-nitropropane. No illness and no skin irritation resulted from applications of either of these compounds to the skin of animals. Machle

TABLE 11

	1-Nitropropane	2-Nitropropane
Boiling point ( $^{\circ}\text{C}.$ ) . . . . .	131.6	120.3
Melting point ( $^{\circ}\text{C}.$ ) . . . . .	-108	-93
Density $d_{20/20}$ . . . . .	1.003	0.992
Refractive index $20^{\circ}\text{C}.$ . . . . .	1.4015	1.3941
Solubility in water		
$20^{\circ}\text{C}.$ (ml./100 ml.) . . . . .	1.4	1.7
Flash point ( $^{\circ}\text{C}.$ ) . . . . .	48.7	39.4
Vapor pressure $20^{\circ}\text{C}.$ (mm Hg) . . . . .	7.5	12.9

found 1-nitropropane to be definitely more toxic on inhalation than either nitroethane or nitromethane. A concentration of  $1\frac{1}{2}$  per cent of the vapor was sufficient to kill all animals exposed and a concentration of 1 per cent caused the death of one monkey. The symptoms and behavior of the exposed animals were similar to those produced by nitroethane, *i.e.*, irritation of the respiratory tract with slow, full respiration and occasional audible râles, conjunctival irritation, and slight salivation. Twitching and jerking movements of the head and extremities were usual with high concentrations. Scott (4) found nitrates in the blood of rabbits intravenously injected with both 1- and 2-nitropropane. Skinner (5), in an investigation of two plants where 2-nitropropane was used in spraying or dipping, found concentrations of this substance varying from 13 to 28 parts per million of the air in one plant and 20 to 45 parts per million in the second plant. The workers in these two plants complained of anorexia, nausea, vomiting, and diarrhea. These symptoms disappeared when methyl ethyl ketone was substituted for 2-nitropropane. On the basis of their study of the physiological response of various species of animals to the vapor of 2-nitropropane, Treon and Dutra (6) have suggested tentatively 50 parts per million as a tolerable limit for human exposure.

### Analysis

Air samples containing nitropropane as a contaminant may be taken by adsorption on silica gel or by the impinger method with isopropyl alcohol. The method of analysis

adopted by Scott and Treon (7) depends upon the reddish-brown color formed when ferric chloride solution is added to an acid solution of the compound. Absorption curves of the colored complex formed with nitropropane may be determined and from these the quantity of nitroparaffin can be estimated.

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### NORISODRINE SULFATE

#### Characteristics

Norisodrine sulfate, N-isopropylarterenol, 1 - (3,4 - dihydroxyphenyl) - 2 - isopropylaminoethyl sulfate,  $(C_{11}H_{17}NO_3)_2 \cdot H_2SO_4$ , crystallizes from acetone-methanol. The crystals have a melting point of 180° C. and are readily soluble in water and in alcohol but are insoluble in ether. The aqueous solution is stable.

#### Uses

Norisodrine sulfate is a drug related to epinephrine and is effective in the treatment of asthma when inhaled as an aerosol or as a fine powder.

#### Toxicity

Watrous and Schulz (1) find that the inhalation of a few milligrams of norisodrine

sulfate may produce side-effects including tachycardia, rise or fall of blood pressure, nausea, precordial pain, anxiety, sweating and tremor. Symptoms are described in three cases of norisodrine absorption occurring in pharmaceutical workers who filled cartridges with the 10 per cent and 25 per cent powder. The symptoms included most of those described above and were transient and nondisabling.

#### Analysis

A chemical method was developed by Watrous and Schulz (1) for determining the atmospheric concentration of norisodrine sulfate sensitive to 1 microgram per liter of air. Concentrations of norisodrine sulfate in the workrooms were found to be below the sensitivity of this method and the symptoms displayed by workers were attributed to sudden high concentrations caused by accidental spillage.

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### OXALIC ACID

#### Characteristics

Oxalic acid, dicarboxylic acid, ethane-diacid,  $HOOC \cdot COOH \cdot 2H_2O$ , is a colorless, crystalline, dibasic acid which, in combination with potassium or calcium, is often found as the crystalline salt in plant cells. The calcium salt constitutes the principle ingredient of certain calculi. Oxalic acid has a density of 1.653, melts at 101° to 102° C., and begins to sublime at about 100° C. Its solubility in water is 83.4 grams per liter of saturated solution at 20° C. and it is moderately soluble in alcohol. When heated with concentrated sulfuric acid, it yields both carbon monoxide and carbon dioxide. It is similarly decomposed by acetic anhydride. With formic acid, oxalic acid yields only carbon monoxide, while no gas at all is given off when it is treated with citric, malic, tartaric, or similar acids. While formerly prepared by treating cellulose material, such as saw-



dust, with sodium hydroxide or by oxidation of such substances with nitric acid, it is now made by the interaction of carbon monoxide and sodium hydrate at about 360° C. Oxalic acid forms a number of monoalkyl esters and dialkyl esters by heating the anhydrous acid with the corresponding alcohol.

### Industrial Uses

The production of oxalic acid in 1954 in the United States amounted to 17,488,000 pounds. Its uses in industry are manifold. It is used as a bleach and cleanser in laundries and as a bleaching agent for straw, leather, and cork, as an ingredient of metal polishes, and to some extent in medicine and photography. Oxalic acid has important applications in calico printing and dyeing and for bleaching woodwork, as well as in celluloid manufacture and the preparation of intermediates and dyes.

### Toxicity

Oxalic acid has long been recognized as a very poisonous substance. Exposure in industry occurs as a result of handling solutions, frequently quite strong, of oxalic acid and also in boiling out automobile radiators, which gives rise to highly disagreeable fumes or mist of oxalic acid causing irritation of the upper respiratory tract. Continued exposure results in a certain amount of systemic poisoning. When a strong solution of oxalic acid is boiled for some time in an average sized room, the room becomes filled with a fog of oxalic acid and this contaminated atmosphere causes coughing and sufficient irritation to make it impossible to continue work for any length of time. The severe cases of systemic poisoning and deaths from oxalic acid mentioned in the literature, however, have usually been related to the ingested substance. In these cases, of which the smallest recorded fatal dose is 5 grams, the symptoms observed have been those of very rapid collapse, with a small, weak pulse following convulsions. The toxic effect, in general, is very rapid in action. At autopsy, there is marked evidence of renal injury with cloudy swelling, hyaline degeneration, and sclerosis of the tubules (1). Grolnick (2) cites the case of a painter who, in the course

of his work, occasionally scrubbed floors with oxalic acid. His hands showed evidence of early gangrene with deep cyanosis from the finger tips to beyond the wrist. The symptoms disappeared on bathing the affected parts with hot, strong solutions of magnesium sulfate. Howard (3) cites the case of an employee of an automobile specialty repair establishment who became afflicted with oxalic acid poisoning from oxalic acid vapors released in boiling automobile radiators. The individual thus exposed was completely disabled for a number of weeks and the symptoms observed were consonant with the symptoms of oxalic acid poisoning. Klauder *et al.* (4) have reported cases of cutaneous reaction following excessive exposure to 5 and 10 per cent solutions of oxalic acid. Lower concentrations however apparently do not have this effect. No maximum allowable concentration value has been established for oxalic acid.

### Analysis

The determination of oxalic acid vapor as an aerial contaminant should be a relatively simple matter in case no complicating substances are also present. Samples can be secured by bubbling through a slightly alkaline solution in a fritted glass bubbler and may subsequently be titrated with dilute standard potassium permanganate solution. Oxalic acid also gives a red double salt of manganese in alkaline solution which can be used for its colorimetric determination (5). The microdetermination of oxalic acid based on the violet-red color produced with 2,7-dihydroxynaphthalene within a range of 200 micrograms has recently been described by Calkins (6).

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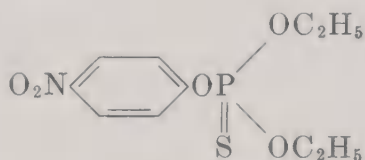
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## PARATHION

### Characteristics

Parathion, O,O-diethyl O-*p*-nitrophenyl thiophosphate, diethyl-*p*-nitrophenyl monothiophosphate



is a colorless and nearly odorless liquid when pure, but the commercial product is brownish and has a garlic-like odor. It boils at 157 to 162 at 0.6 millimeter, has a density of  $d_{25/4}$  1.26 and a refractive index of  $n_{20/D}$  1.53668. While nearly insoluble in water (20 parts per million) it dissolves freely in alcohol, ether, and aromatic hydrocarbons.

### Uses

Parathion is an important agricultural insecticide and production of this substance in the United States amounted to 3,889,000 pounds in 1954 (1).

### Toxicity

The unique toxic qualities of the organic phosphorus insecticides are well-exemplified by parathion. In general these substances appear to be toxic to animals because of their interference with the normal mechanism of nerve impulse conduction. Fatal effects are produced by cholinesterase depletion in the blood stream and tissue fluids. Symptoms of poisoning do not appear until the level of cholinesterase activity falls below about 30 per cent, after which the toxic effects suddenly appear. Parathion is one of the most toxic of the organic phosphorus insecticides, the acute oral  $LD_{50}$  value for rats being 6 milligrams per kilogram of body weight. Furthermore, many of these substances, parathion in particular, are ab-

sorbed through the skin and are therefore especially hazardous. Numerous cases of poisoning and several fatalities have been reported from contact with parathion and numerous investigations have been reported concerning its action. In general it may be said that the toxicity of the organic phosphorus insecticides is largely a function of their anticholinesterase activity. Frequent measurement of blood cholinesterase levels has been a routine procedure where contact with the poison has occurred. Atropine is generally recommended as a specific antidote for the organic phosphorus poisons.

Tetraethylpyrophosphate,  $(C_2H_5)_4P_2O_7$ , is rated as more acutely toxic than parathion, since it has an oral  $LD_{50}$  value of 2 milligrams per kilogram of body weight. However, unlike parathion, chronic effects are less evident with tetraethylpyrophosphate as it is rapidly hydrolyzed in the body and leaves no toxic residue. Chronic poisoning with parathion, on the other hand, results in gradually reduced cholinesterase levels and very slow regeneration of cholinesterase after removal from contact with the toxicant.

### Analysis

Hirt and Gisclard (2) describe a sensitive method for the determination of parathion concentration as airborne dust, mist, or vapor in workroom atmospheres. This method consists in sampling in ethanol and subsequent ultraviolet spectroscopic analysis. The detectability is stated to be 9 micrograms when a 50 millimeter absorption cell is used. Richards (3) has modified Frazier's original method (4) for determination of parathion air samples, which depends upon decomposition of the parathion and estimation of the phosphate content colorimetrically. According to Biggs (5) the analysis of parathion as determined by direct measurement of its characteristic absorption spectrum may be confirmed by its hydrolysis to *p*-nitrophenol and measurement of the latter's absorption spectrum.

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## PENTACHLOROETHANE

### Characteristics

Pentachloroethane,  $\text{CHCl}_2 \cdot \text{CCl}_3$ , is a heavy, colorless liquid having a boiling point of  $160.5^\circ \text{C}$ ., a density  $d_{20/4}$  of 1.681, and refractive index  $n_{20/D}$  of 1.5024. It has an evaporation rate of 3 in comparison with 100 for ether and its solubility in water at room temperature is 0.5 gram per liter. Pentachloroethane is prepared by the chlorination of trichloroethylene, ethyl chloride, or tetrachloroethane. Distillation at atmospheric pressure causes some decomposition and on boiling with alcoholic potash, tetrachloroethylene (boiling point  $121^\circ \text{C}$ .) is formed.

### Industrial Uses

Pentachloroethane is principally used for the dry cleaning of clothes. However, its application for this purpose is minor compared with some hydrocarbons. To some extent, pentachloroethane has been used as a solvent for cellulose acetate, as well as certain cellulose ethers, and for resins and gums.

### Toxicity

Pentachloroethane is somewhat more toxic than tetrachloroethane. In general, it is narcotic in action and is more effective in this respect than chloroform. It has a pronounced irritating effect on mucous membranes, causing purulent inflammation of the nose, throat, and respiratory passages. Chronic poisoning causes fatty degeneration of the liver, inflammation of the kidney, bronchitis, pronounced hyperemia of the lungs, and purulent pneumonia. Pentachloroethane is regarded by Kiessling

(1) as 20 times as potent as chloroform as a narcotic and 26 times as toxic as chloroform for the isolated heart. Although Henderson and Haggard rate the toxicity of pentachloroethane as high in comparison with other chloro derivatives of methane and ethane, these authors point out the inadequacy of this type of comparison (2), especially where one toxic agent is predominantly a central nervous system poison and the other primarily impairs the liver function. No maximum allowable concentration value for pentachloroethane has been established.

### Analysis

The ordinary flame detector is useful in detecting the presence of pentachloroethane as an atmospheric contaminant. The amount of this substance in air may be indicated by its reaction with pyridine and sodium hydroxide (3). Quantitative evaluation of the atmospheric concentration may also be made by Setterlind's combustion-titration method (4).

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## PENTACHLOROPHENOL

### Characteristics

Pentachlorophenol,  $\text{C}_6\text{Cl}_5\text{OH}$ , density  $d_{22/4}$  1.978, melting point  $190^\circ$  to  $191^\circ \text{C}$ ., boiling point  $309^\circ$  to  $310^\circ \text{C}$ . (with decomposition), forms white, needle-like crystals. The solubility in water is very slight (0.018 gram per liter at  $27^\circ \text{C}$ .) (1). It is, however, readily soluble in such solvents as methyl and ethyl alcohol and, to some extent, in benzene, ethylene glycol, and Stoddard solvent. Pentachlorophenol has a very low

vapor pressure at ordinary temperatures. At 20° C., the vapor pressure is  $1.7 \times 10^{-4}$  millimeters of mercury and at 50° C. is only  $3.1 \times 10^{-3}$  millimeters of mercury. The sodium salt of pentachlorophenol, commercially called Dowicide G, is soluble in water (33 grams per 100 grams at 25° C.), in acetone (37 grams per 100 grams at 37° C.), and in ethyl alcohol (64 grams per 100 grams at 25° C.). The salt occurs in commerce as buff-colored flakes and is practically odorless.

### Industrial Uses

Owing to its toxicity to fungi, bacteria, yeasts, and other microorganisms, pentachlorophenol has received wide application in the field of industrial preservation. Its high degree of toxicity to different types of organisms, its low solubility in water and low vapor pressure (which insures permanence), its good chemical stability, and its relatively low cost has made it particularly useful in industry. Wood preservation, sap stain control, slime and algae control, the preservation of glues, gums, and such proteins as casein, albumin, and gluten, the preservation of hemp, jute, and other cellulosic products, as well as textiles in general, and the preparation of fungus-resisting paints constitute industrial application of this substance or its sodium salt.

### Toxicity

The smallest lethal dose of sodium pentachlorophenate in aqueous solution or in 1 per cent sodium chloride solution when applied to the skin was found by Kehoe and his associates (2) to be 257 milligrams per kilogram expressed in terms of free pentachlorophenol. When administered by mouth, the corresponding dose was found to be 218 milligrams per kilogram, and when given intravenously, 22 milligrams per kilogram. No indication of chronic poisoning was found. Acute and chronic poisoning of rabbits with sodium pentachlorophenate was investigated by Boyd and his associates (3) and McGavack *et al.* (4) in which toxicity by oral, subcutaneous, and intraperitoneal routes of administration was studied. These investigators state that contact dermatitis

represents the most likely industrial hazard. Skin contact over a period of 14 days with 1 per cent solutions caused erythema and with 1.5 per cent caused microscopic evidence of skin irritation. Greater concentrations caused gross changes—edema inflammation, and eventual “tanning”. Deichmann and his associates (5) and Machle and his associates (6) found that pentachlorophenol can be absorbed through the skin into the blood. Pentachlorophenol is but little likely to emit harmful vapors when cold because of its high boiling point. When heated, however, this substance gives rise to highly pungent odors and irritant fumes. Its dust is also irritating. Urinary determination of pentachlorophenol has been suggested (6) as a means of estimating the extent of human absorption and consequently the severity of exposure to pentachlorophenol. Truhaut and his associates (7) have investigated the toxicology of pentachlorophenol experimentally with animals and also report a number of cases of human poisoning in the wood industry with two fatalities.

### Analysis

Since the vapor pressure of pentachlorophenol is low at room temperature, the amount present as an aerial contaminant, and hence its detection as fume vapor, is unimportant. However, either pentachlorophenol or its sodium salt may be spread in the atmosphere as dust. The determination of pentachlorophenol in air would require the catalytic decomposition of the contaminant by passing it over platinum at 1000° to 1100° C., followed by absorption and estimation of the hydrogen chloride formed. Deichmann and Schafer (8) have developed a spectrophotometric method for estimating pentachlorophenol in tissues and water. This method is based upon the determination of a reddish-yellow pigment formed by the action of fuming nitric acid on pentachlorophenol. Truhaut *et al.* (9) steam-distil biological material to separate pentachlorophenol, then oxidize with nitric acid and permanganate followed by titration with silver nitrate.

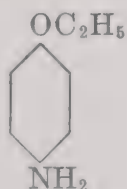


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***p*-PHENETIDINE****Characteristics**

*p*-Phenetidine, 4-aminophenoethyl ether, 4-aminophenetole, aminoethoxy benzene, ethoxyaniline



is a colorless liquid which slowly turns reddish brown on exposure to air and light. It is usually prepared from 4-nitrophenetol by the action of tin or iron and hydrochloric

acid, or by stannous chloride and hydrochloric acid. Its melting point is about 3° C., boiling point 254.7° C. and density  $d_{15/4}$  1.0613. It is insoluble in water and is only slightly volatile with steam. It is soluble in alcohol and other organic solvents.

**Uses**

*p*-Phenetidine is an important chemical intermediate and is used in the manufacture of a number of drugs (phenacetin, lactophenin, and holocain) as well as in the dye-stuff industry. It is also used in the manufacture of the very sweet substance called dulcin. The *o*- and *m*-phenetidines are relatively much less important than the *p* compound.

**Toxicity**

Although *p*-phenetidine is a toxic substance, comparatively little investigation of the physiological response to this substance had been reported prior to the investigation of Smith and Williams (1) on the metabolism of this compound. *p*-Phenetidine has some bactericidal action and has a salicyl index number of 80 (2), but it has very little importance in this respect. The early experimental work showed *p*-phenetidine to be more poisonous than phenacetin. When administered to rabbits in doses of 1 to 2 grams it produces pronounced symptoms of poisoning—in particular hemoglobinemia. In dogs at a dosage of 0.5 gram per kilogram of body weight it produces vomiting, extreme irritation of the alimentary tract, and nephritis (3). In man, administration by mouth causes cyanosis and hypothermia. According to Edlefsen (4) *p*-phenetidine as such is excreted in the urine only following large doses and this accounts for Müller's negative results following small doses and its detection as a metabolism end product following acetophenetidine administration (5). Smith and Williams (1) have recently made a more complete investigation of the detoxication mechanism which is effective following administration of *p*-phenetidine to rabbits. About 30 per cent of the phenetidine fed is excreted as ethereal sulfates. The main phenolic substance in the sulfate fraction is 2-hydroxy-4-ethoxyaniline. The *p*-pheneti-

dine undergoes de-ethylation acetylation and oxidation within the body. A considerable amount of glucuronide is excreted and, among other substances, *p*-acetamidophenyl glucuronide in 6 per cent yields was isolated from the urine. While *p*-phenetidine has not so far been reported as a cause of industrial injury, it should be recalled that it is absorbed through the skin and that exposure to its vapor is hazardous unless suitably controlled.

### Analysis

No method has been developed for the determination of minute amounts of *p*-phenetidine as an atmospheric contaminant. However, small amounts of the hydrochloride give a red color with ferric chloride, which later turns to violet. With calcium hypochlorite it gives a red-colored precipitate (6). Edlefsen (7) detected *p*-phenetidine in urine by diazotizing and coupling with  $\alpha$ -naphthol. A deep red color is formed which makes the estimation of *p*-phenetidine in this case a simple colorimetric procedure.

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## PHENOL

### Characteristics

Phenol, hydroxybenzene, carboic acid,  $C_6H_5OH$ , is a colorless solid with melting point  $42^\circ C.$ , boiling point  $183^\circ C.$ , specific gravity 1.071, and index of refraction 1.5425 at  $41^\circ C.$  One part is soluble in 15 parts water at  $16^\circ C.$ , while at  $66^\circ C.$ , it is soluble in

all proportions. Phenol volatilizes with steam. It gives a violet color with ferric chloride in water. Nitration with hot fuming nitric acid yields picric acid (2,4,6-trinitrophenol) with a melting point of  $122^\circ C.$  With bromine water, phenol forms tribromophenol with a melting point of  $93^\circ C.$  Phenol, when heated with phthalic anhydride and a drop of concentrated sulfuric acid, yields phenolphthalein which gives a deep red color with dilute alkali.

### Industrial Uses

In 1935, the total U. S. production of phenol was 43,418,579 pounds, half of which represented synthetic production. In 1947, the total United States production of phenol was 268,460,000 pounds, 245,000,000 pounds of which represented synthetic production and 23,500,000 pounds of which was derived from fractional distillation of coal tar. Production in the United States in 1954 amounted to 417,503,000 pounds. A plant has been constructed for the synthetic production of phenol capable of producing at least 20,000,000 pounds of phenol per annum from benzene (1). In a more recently developed continuous process, phenol is made from monochlorobenzene (2). Among the many uses for phenol in industry, one finds its greatest use in the manufacture of synthetic resins and plastics (60 to 65 per cent). Insecticides and disinfectants absorb about 10 per cent and the extraction of lubricating oils and the manufacture of dyes and intermediates each absorb about 5 per cent. Among other uses are the manufacture of perfumes, pharmaceuticals, explosives, and disinfectants.

### Toxicity

Phenol exerts a strong corrosive action on body tissues and produces severe systemic reactions after absorption through the skin and mucous membranes, the gastrointestinal tract, or the lungs. It is a general protoplasmic poison, particularly affecting the central nervous system. Serious burns may result from skin contact unless the chemical is removed promptly and thoroughly. Dermatitis may result from repeated or prolonged contact with low concentrations of phenol in



any form. It causes about 20 per cent of the dermatitis cases of the phenolformaldehyde industry (3). Absorption may occur through the unbroken skin. The symptoms of chronic phenol poisoning are: digestive disturbances, nervous disorders, and skin eruptions. Chronic poisoning may terminate fatally in cases where damage to the liver or kidneys is extensive. Following absorption, it is partly oxidized to hydroquinone and pyrocatechin, which are excreted in the urine and tend to be oxidized to color substances, which give the urine a dusky-green color, changing to brown or even black. The maximum allowable concentration value for the vapor of phenol in air is 5 parts per million. The symptoms of acute toxicity from phenol absorption are: profound muscular weakness, headache, dizziness, dimness of vision, ringing in the ears, irregular and rapid respiration, weak pulse, and difficult breathing. Any or all of these toxic effects may result from absorption. Phenol taken internally is a violent poison for which there is no known satisfactory antidote. As little as 8.5 grams has caused death. The maximum therapeutic dose is 200 milligrams (4), while the average dose is 60 milligrams.

### Analysis

Phenol may be separated from a variety of substances by steam distillation of the acidified material. A method which may be applied to macro quantities is based on the formation of tribromophenol by the bromination of phenol with the bromine solution produced by the use of a potassium bromide-potassium bromate mixture (5). An excess of bromine is used forming tribromophenol and the excess is determined by adding potassium iodide and back-titrating with sodium thiosulfate. Phenol in trace amounts (5 to 100 micrograms per liter of solution) is best determined colorimetrically. Phenol, and most phenolic compounds in which the *p* position is unsubstituted, form blue 2,6-dibromoindophenols in combination with 2,6-dibromoquinone chloroimide (6, 7). It couples with diazotized sulfanilic acid to form highly colored azophenol dyes. The color should reach maximum value within 30 minutes, although very low concentra-

tions of phenol may require longer standing and some error may occur in this case, owing to oxidation of the reagent.

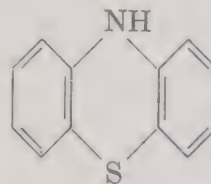
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## PHENOTHIAZINE

### Characteristics

Phenothiazine, dibenzthiazine, thiodiphenylamine, phenoxur



is a grayish-green powder in its commercial form and crystallizes as yellow to colorless rhombic leaflets from toluene or alcohol. It is prepared by the reaction of diphenylamine and sulfur, preferably in the presence of an oxidizing catalyst. Phenothiazine melts at 184 to 185° C. and sublimes at 371° C. It is insoluble in water but readily soluble in benzene and is slightly soluble in alcohol and in mineral oil.

### Uses

Phenothiazine has great practical importance as the parent substance of the thiazine dyes, including methylene blue, brilliant alizarin blue, and thionine blue. It is extensively used as an insecticide and to some extent as an anthelmintic, as well as in chemical manufacturing. The extent to which it is used is indicated by the produc-

tion figures of 2,343,000 pounds in the United States in 1949 and 5,914,000 pounds in 1952.

### Toxicity

While the toxicity rating for phenothiazine is rather low, it possesses the undesirable characteristic of inducing photosensitization in individuals exposed to it. Furthermore, it is irritating to the skin. Guinea pigs appear to be the most sensitive of laboratory animals with reference to exposure to phenothiazine (1). This substance has been used as an insecticide for a number of years and is not only toxic to the codling moth and to the roach *periplaneta americana* (2), but also to anopheles larvae (3), although damaging to bees and fish. Phenothiazine has been extensively used both in animals and in man for controlling pinworm and roundworm infestation and other nematode infections, and particularly in horses and sheep. Most (4) treated over 200 patients with phenothiazine without apparent ill effects, the total dose averaging 0.3 gram per kilogram of body weight. However, larger doses may be quite toxic and produce hemolytic anemia and hepatitis. DeEds and his associates (5) investigated the metabolism of phenothiazine and found that the urine of animals ingesting this substance contained leucothionol and some form of water-soluble phenothiazine, possibly conjugated, or in some loose chemical composition. Leucophenothiazine potassium sulfate (6), thionol (7) and a conjugate composed of leucothionol and glucuronic acid have been identified as end products of phenothiazine metabolism.

Skin irritation from phenothiazine is a result of photosensitization presumably induced by the presence of the oxidation-reduction system thionol-leucothionol in the tissues (8). Men working with this substance and not exposed to direct sunlight are not affected apparently. However Fleischhacker (9) has reported four cases of dermatitis in workers engaged in tabletting phenothiazine. Sunlight exposure in the plant or after hours was not reported. However, fruit sprayers complain of intense itching and reddening of the skin, sometimes accompanied by edema and secondary in-

fection on areas of intense hyperemia and occasionally requiring hospitalization. Whitten and his associates (10) have reported a photosensitized keratitis due to the action of light on the cornea and which occurs 12 to 36 hours after dosing.

### Analysis

Commercial phenothiazine may contain as many as five different compounds and requires purification by solution in benzene and absorption of impurities by passing it through a column of alumina (11). The phenothiazine may be estimated colorimetrically following oxidation with bromine water and comparison with known quantities of the pure substance.

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## PHENYLENEDIAMINE

### Characteristics

Phenylenediamine, diaminobenzene,



exists in three forms (*o*, *m*, and *p*). The



physical properties of these substances are indicated in Table 12.

The three phenylenediamines are solids which crystallize well, but as they oxidize readily they cannot be kept indefinitely in air for they become colored and decompose. Their salts are more stable. *o*-Phenylenediamine is prepared by the reduction of *o*-nitroaniline with iron and hydrochloric acid or with zinc dust and alkali. The *m* compound is similarly prepared from *m*-dinitrobenzene and the *p* from *p*-nitroaniline.

### Industrial Uses

*o*-Phenylenediamine has only a limited technical use. *m*-Phenylenediamine and its derivatives containing methylated or phenylated amino groups are important substances, however, since they are used for the synthesis of dyes, particularly azo dyes. This group is used for the development of the diazotized dye directly on the fiber and also finds some application as a reagent for detecting nitrous acid. *p*-Phenylenediamine is also employed for the synthesis of various dyes and for the dyeing of dead hair and furs and as an accelerating agent in the vulcanization of rubber. *p*-Phenylenediamine is also used as a fine-grain developer in photography. During 1945, 1,010,000 pounds of *m*-phenylenediamine were produced in the United States. The latest figures available for *o*- and *p*-phenylenediamine show that in 1953, 1,058,000 pounds were produced.

### Toxicity

Of the three phenylenediamines, *p*-phenylenediamine has proved to be an especially virulent skin irritant. It has been used under the trade name of Ursol D for the dyeing of furs and also has been employed as a hair dye, although it has been banned for this purpose in France, Germany, and Austria. According to White (1), repeated application of basic *p*-phenylenediamine or Ursol causes the development of an eczematous-like eruption and the whole of the skin becomes sensitive. According to Hanzlik (2), *p*-phenylenediamine salts are nonirritant in contact with the unbroken skin, but hypodermic and gastric administration of this

TABLE 12

Substance	Melting Point °C.	Boiling Point °C.	Density	Solubility in Water (Grams per 1000 Grams Sat. Solution)
<i>o</i> -Phenylenediamine	102	257	—	40.5 at 35.1°C.
<i>m</i> -Phenylenediamine	63	283	1.1389	838.3 at 34.4°C.
<i>p</i> -Phenylenediamine	140	267	—	98.5 at 37.8°C.

substance produces a peculiar specific edema of the face, nose, tongue, conjunctiva, and neck. The asthma and respiratory symptoms of workers in the fur dye industry in which *p*-phenylenediamine is used are due to direct irritation and bronchial stimulation, rather than to anaphylaxis. Mayer and Förster (3), upon examination of 181 workers employed in the fur trade where *p*-phenylenediamine was used as a dye, found that 111 individuals suffered from dermatitis or asthma. Cases of occupational asthma among fur workers using *p*-phenylenediamine have occurred with such frequency in Germany that the disease has become known as "Ursol asthma". It is characterized by rhinitis, attacks of paroxysmal coughing, a sensation of oppression in the chest, special sensations of smell, and bronchial asthma. Local skin irritation is occasionally reported in workers using *p*-phenylenediamine developers for photographic purposes. The patch test with *p*-phenylenediamine is highly specific for occupational dermatitis due to this dye among workers in the fur industry. Silverberg and Heimann (4) found that scratch tests with *p*-phenylenediamine on asthmatics in the fur industry were negative, but that four of the ten asthmatics examined gave a positive reaction to the patch test with *p*-phenylenediamine. Patch tests with *p*-phenylenediamine on fur workers who had neither asthma nor occupational dermatitis were negative. Hunter (5) cites cases of systemic poisoning and one death arising from the use of this substance in hair-dressing establishments. He reported several cases of anemia following the use of *p*-phenylenedi-

amine as a hair dye. This anemia is characterized by its indifference to treatment with iron or liver extract. The simultaneous excretion of coproporphyrins I and III in these cases indicates disturbances in pigment metabolism similar to those found in diseases of the liver and in some forms of exogenous poisoning, but unlike those found in pernicious anemia and hemolytic jaundice. While the formation of methemoglobin is delayed *in vivo*, the changes in red corpuscles produced *in vitro* by phenylenediamine can be duplicated with this substance *in vivo* in cats, dogs, guinea pigs, and rabbits (6). No maximum allowable concentration value has been established for any of the phenylenediamines.

### Analysis

Although no direct method for the determination of the phenylenediamines as aerial contaminants has been proposed, the reactivity of these substances with various metal ions can be utilized for their evaluation. *m*-Phenylenediamine reacts with chromates to give a red-brown coloration in both neutral and acid solution, while in ammoniacal solutions the color changes to yellow. With nitrites, the dye Bismarck brown is formed which is intensely colored. Copper salts yield a rose-red colored solution. *p*-Phenylenediamine on oxidation with hydrogen peroxide or hypochlorite yields a diiminoquinone having a violet color.

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## PHENYLHYDRAZINE

### Characteristics

Phenylhydrazine, hydrazinobenzene,



is a colorless, refractive oil at room temperature, but, when pure, it sets to a crystalline mass at 19° C. The crystalline plates or prisms have a melting point of 23° C. and the liquid boils at 240 to 241° C. Its density is  $D_{20.5/4}$  1.0978 and index of refraction  $n_{20/D}$  1.60813. It is a weak base, sparingly soluble in water or ligroin, but readily soluble in alcohol, ether, chloroform, or benzene. It may be purified by crystallization from alcohol, or by distillation *in vacuo*. However, it becomes brown rapidly on exposure to air. It is volatile with steam and forms a stable hydrochloride which can be crystallized unchanged from water. Commercially phenylhydrazine is prepared by treating benzene diazonium chloride with sodium sulfite and then reducing the mixture with zinc dust and acetic acid. It can also be prepared by reduction of diazonium chloride with stannous chloride.

### Uses

Phenylhydrazine is a valuable reagent in the organic chemical laboratory for the identification of compounds containing ketonic groups, the product of these reactions being hydrazones. Compounds containing the grouping  $-\text{CHOH}-\text{CO}-$ , for instance, glucose, fructose, etc., react with 2 molecules of phenylhydrazine to yield characteristically crystallized osazones. In addition to its analytical application, phenylhydrazine is used for synthetic organic purposes in the manufacture of dyestuffs, intermediates, pharmaceuticals and nitron—a stabilizer for explosives.

### Toxicity

The toxicity of phenylhydrazine by mouth is not remarkable and in fact phenylhydrazine has been recommended for therapeutic purposes in the treatment of polycythemia vera in dosages of 0.1 to 0.2 gram. However this therapeutic application has been decried by Cushny as dangerous. It has been demon-



strated repeatedly that phenylhydrazine produces anemia when fed to or injected into animals (1, 2, 3). Allen and Page (3) concluded that the erythrolytic effect of phenylhydrazine was due to the benzene nucleus and not to the hydrazine portion of the molecule. In acute poisoning of the rabbit and guinea pig hemolysis is well marked (4), the urine is diminished in quantity and is dark in color. Intense anemia, loss of appetite, and asthenia mark the general condition. Chronic poisoning of young animals results in a checked and irregular growth, anemia, and asthenia (5) with no apparent alteration in the volume of urine. At autopsy an increased deposition of iron in the liver, spleen, and kidney was noted. According to Hesse and his associates (6) 0.02 gram of phenylhydrazine per kilogram of body weight when administered subcutaneously in dogs invariably results in death in about 22 days. According to these investigators the cause of death is a depletion of glycogen, especially in the heart muscle. An experimental study of the mechanism of detoxication revealed that glycogen formers, or substances promoting glycogen synthesis, are certain remedies against fatality, the animals remaining obviously healthy following this treatment.

While no industrial fatalities have been recorded from contact with phenylhydrazine, cases of skin irritation occasionally occur in industry and it should be emphasized that it is not only a skin poison but that absorption from the skin occurs very readily. Von Oettingen and his associates (7), in a study of the relation between the chemical constitution and pharmacological action of phenylhydrazine derivatives, investigated the physiological response to these substances with particular reference to their toxicities and irritant effects on the skin. Von Oettingen (8) further discussed the potential danger of phenylhydrazine-zinc chloride and made recommendations for the prevention of accidents in handling this material. Dermatitis from phenylhydrazine-zinc chloride was later reported by Downing (9) in a rubber mill employee. Tests showed this individual to be sensitized to phenylhydrazine following a brief exposure. Three

additional cases of phenylhydrazine poisoning in industry have been reported by Rukl (10). Each of these cases was due to skin absorption.

### Analysis

While no method has been proposed for the analysis of air containing phenylhydrazine mist or vapor, it is possible that the method of Ling and Nanji (11) could be modified for this purpose. In this method phenylhydrazine may be estimated volumetrically by its reaction with excess of iodine and subsequent determination of the iodine consumed by titration with thiosulfate.

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## PHENYLPHENOL

### Characteristics

Phenylphenol exists as *o*-phenylphenol (2-hydroxydiphenyl), *m*-phenylphenol (3-

hydroxydiphenyl), and *p*-phenylphenol (4-hydroxydiphenyl),  $C_6H_5 \cdot C_6H_4 \cdot OH$ . These substances are also known as orthoxenol, metaxenol, and paraxenol, respectively. All three crystallize in needle form, the *o* form from petroleum ether, the *m* form from water in which it is slightly soluble, and the *p* form from alkaline solution. The *o* and *p* forms are commercially important. *o*-Phenylphenol boils at  $280^\circ C.$ , melts at  $55.5$  to  $57.5^\circ C.$ , and is insoluble in water but very soluble in ether. *p*-Phenylphenol melts at  $164$  to  $165^\circ C.$ , boils at  $305$  to  $308^\circ C.$ , and is similar to the *o* form in solubility. *m*-Phenylphenol melts at  $75^\circ C.$ , and is very soluble in alcohol.

### Uses

*o*-Phenylphenol is used as a fungicide and germicide and is known commercially as Dowicide. Both the *o* and the *p* forms are used in the rubber industry.

### Toxicity

Hodge and his associates (1) found the acute oral toxicity  $LD_{50}$  of *o*-phenylphenol for rats to be 2.7 gram per kilogram of body weight. Rats maintained for 2 years on a diet containing up to 0.2 per cent of *o*-phenylphenol were not adversely affected. When the amount of *o*-phenylphenol was increased to 2 per cent, however, a slight retardation of growth was noted and in addition some kidney changes and deposition of *o*-phenylphenol in the kidney. In another series of experiments dogs were fed a diet containing 0.5 gram per kilogram of body weight of *o*-phenylphenol daily for a period of 1 year with no adverse effects. It is apparent therefore that the acute oral toxicity of *o*-phenylphenol is rather low.

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## PHTHALIC ANHYDRIDE

### Characteristics

Phthalic anhydride,  $C_6H_4(CO)_2O$ , is a white crystalline substance obtained by the

dehydration of phthalic acid, an aromatic polybasic organic acid derived from naphthalene. Its specific gravity is 1.527 ( $4^\circ C.$ ). It melts at  $130.8^\circ C.$  and boils at  $295.1^\circ C.$ , giving a dense white fume which crystallizes in long white needles. It is soluble in 162 parts of water at room temperature, dissolving more readily in hot water with conversion into phthalic acid, and it is soluble in 125 parts of carbon disulfide. While sparingly soluble in ether, it is more readily soluble in alcohol. It is prepared by the oxidation of naphthalene with a mixture of mercuric sulfate and cupric sulfate in the presence of sulfuric acid or by passing naphthalene and oxygen over a catalyst at  $400^\circ$  to  $500^\circ C.$  Vanadium pentoxide has been found to be a useful catalyst for this purpose. About 130 pounds of phthalic anhydride is derived from 100 pounds of naphthalene.

### Industrial Uses

The production of phthalic anhydride in the United States for 1945 amounted to 125,033,000 pounds, which was somewhat in excess of that (124,473,000 pounds) in 1944. Of the total amount produced in the latter year, 55.3 per cent was used in the form of esters as plasticizers (largely in the form of dibutyl phthalate); 30.6 per cent in resins, principally of the alkyd resin type; 8.8 per cent in dyestuffs; and 2.5 per cent in drugs (1). Production in the United States had increased to 253,847,000 pounds in 1954. Among other special uses are the manufacture of phthaleins, benzoic acid, synthetic indigo, and the artificial resin, Glyptal. An increased use of phthalic anhydride has resulted from the recent discovery of the effectiveness of dimethyl phthalate as an insect repellent.

### Toxicity

Very little investigation of the toxicity of phthalic anhydride fume has been made. The fume is rather a disagreeable substance to breathe, having a choking effect and a characteristic odor. Long-continued exposure even to relatively low concentrations of the fume would doubtless prove irritating to the mucous surfaces. Policard



and his associates (2), for instance, finds that workers exposed to phthalic anhydride dust experience nasal irritation, asthenia, and frequent conjunctivitis. However, there is no record of injury following short exposure to relatively high concentrations. Acute dermatitis which occurred in a plant producing phthalic anhydride was attributed by Kito and Tosu (3) to the presence of naphthoquinone in the crude product. The phthalic acid esters, according to Lehmann (4), are practically without danger. Shaffer and his associates (5), in an investigation of the toxicity of di(2-ethylhexyl) phthalate, found that its toxicity is largely or entirely due to the alkyl portion of the molecule rather than to the phthalic acid.

### Analysis

Phthalic anhydride or phthalic acid may be identified by converting it to fluorescein which is distinguished by its powerful green fluorescence. When mixed with an equal weight of resorcinol, moistened with sulfuric acid, heated to 160° for 3 minutes, cooled, and treated with sodium hydroxide solution, the diluted phthalic anhydride gives the characteristic fluorescein reaction. On fusion with aniline at 250° C., washing with an alcoholic solution of chloroform, and precipitation with alcohol, a crystalline deposit of white needles of phthalanil (melting point 207° C.) is formed. When present as an atmospheric contaminant, phthalic anhydride may be absorbed in dilute sodium hydroxide solution and titrated, provided it is the only acid contaminant, or it may be separated as lead phthalate in alcoholic solution (6). An indirect method would be required in this case, for the lead phthalate precipitate usually contains some basic salt.

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## PICRIC ACID

### Characteristics

Picric acid, 2,4,6-trinitrophenol,  $C_6H_2 \cdot OH(NO_2)_3$ , crystallizes from water in bright yellow plates which melt at 122° C. and have a density of 1.767. Its solubility in water at 25° C. is 14 grams per liter and 68 grams per liter at 100° C. In benzene at 20° C., the solubility is 53 grams per liter. Picric acid is characterized by its bitter taste, strong acid properties, its yellow color, and its tendency to stain protein material yellow. It is considerably ionized in aqueous solution approaching the mineral acids in acidity and ability to form metallic salts or picrates. The salts of picric acid crystallize well and several of them, such as the ammonium and potassium salts, are difficultly soluble in water. These salts explode if struck when dry. The iron, nickel, and chromium picrates are very sensitive to impact and are used as detonators. Lead picrate is even more dangerous as it is sensitive to both heat and shock. Ammonium picrate is less sensitive to shock than picric acid and is free from the disadvantage the latter has of forming explosive metal salts in contact with metallic substances. Since it has a high melting point (270° C.), it cannot be used for shell filling by casting but is used as a charge for armor-piercing shells where it explodes under detonation after the shell has penetrated. Picric acid is made by the nitration of phenol which has previously been treated with sulfuric acid to form phenol-sulfonic acid. Ammonium picrate is formed by neutralizing picric acid with ammonia. The acid unites readily with a number of organic substances and is therefore very useful in their identification.

### Industrial Uses

Picric acid, though used extensively as a military explosive, has the serious disad-

vantage that it corrodes the metal surfaces of shells with the formation of highly sensitive metallic derivatives. The dried picric acid is packed into shells or it is melted with an added substance to lower the melting point. Since picric acid stains proteins yellow, it is used as a bright yellow dye for silk and wool in the textile industry. It is the starting point in the manufacture of nigrosine and indulene dyes and is also used in medicine as an astringent and germicide and in the treatment of burns. Picric acid is used in the manufacture of matches and in the leather industry, as well as a textile mordant. It is also used as a chemical reagent.

### Toxicity

Exposure in industry is by skin contact or by inhalation of the dust of picric acid or its salts. The toxicology is of practical importance especially in the manufacture of munitions. Skin contact with the dry powder of picric acid or ammonium picrate powder causes sensitization dermatitis among workers exposed to it (Schwartz). The face is usually involved especially around the mouth and sides of the nose. There are edema, papules, vesicles, and, finally, desquamation (1). The systemic poisoning following the absorption of picric acid causes symptoms of headache, vertigo, nausea, vomiting, and diarrhea. Yellow coloration of the skin and conjunctiva may occur and there may be darkened or port wine colored urine and albuminuria. Toxic doses cause destruction of the erythrocytes and produce gastroenteritis, hemorrhagic nephritis, and acute hepatitis. Part of the picric acid may be excreted unchanged in the urine, but most of the picric acid is converted into picramic acid which is then excreted in the urine and may be revealed by Le Methonard's test for picramic acid. Sunderman and his associates (2), after study of a small selected group of workers in an ammonium picrate plant, found that the most common health problem was dermatitis. Upper respiratory disease was negligible and systemic toxicity was not recognized among the workers. However, experimental animals severely exposed to ammonium picrate dust showed definite injury to certain tissues. Brown granular deposits,

presumably picrate, were found widespread particularly in the lungs, liver, heart muscle, kidney, and circulating blood. Sunderman and his associates (2) found that dermatitis developed only among workers least exposed to ammonium picrate dust, which lends support to the opinion that desensitization or adaptation may occur following exposure similar to that occurring with teteryl. An interesting case of mass poisoning from ingested picric acid reported in 1946 occurred at a naval anchorage in Japan in which naval personnel were poisoned following the ingestion of drinking water containing picric acid as an impurity (3). Picric acid dumped near the naval anchorage at Wakayama was pumped into a ship's still and was carried over with the vapor phase into the fresh water supply inducing hematuria among those drinking the water. No maximum allowable concentration value for picric acid dust has been established.

### Analysis

Air samples containing the dust of picric acid or ammonium picrate may be collected in impingers containing ethyl alcohol as the collecting medium. In the method of Sunderman and his associates (2) for the quantitative determination of ammonium picrate in atmospheric samples, the alcoholic solution of the collecting medium was made up to a definite volume and directly read in a Klett-Summerson photoelectric colorimeter fitted with a blue filter for maximum transmission at 420 millimicrons. Picric acid on reduction by ammonium sulfide in alcohol or by zinc dust in ammonium hydroxide yields 4:6-dinitro-2-aminophenol (picramic acid) having a melting point of 168° C. With phosphorus pentachloride, picric acid yields picryl chloride, melting point 83° C. Picric acid also forms addition compounds with benzene, melting point 84° C. and with naphthalene, melting point 149° C.

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## PIPERONYL BUTOXIDE

### Characteristics

Piperonyl butoxide, 6(propyl piperonyl)-butyl carbityl ether, 3,4-methylenedioxy-6-propylbenzyl butyldiethylene glycol ether, is a substance that was introduced as a synergistic agent for the pyrethrins. According to Wachs (1) it may be synthesized by reacting the chloromethyl derivative of dihydrosafrole with the sodium salt of mono-*n*-butyl ether of diethylene glycol.

### Uses

Piperonyl butoxide increases the toxic effect of pyrethrins and increases the length of time that the insecticides remain effective. Although there is no evidence of combination of the two insecticides, their association has proved particularly effective against a variety of insects.

### Toxicity

Piperonyl butoxide has been shown to have a relatively low order of toxicity against warm-blooded animals. The LD<sub>50</sub> dose for rats has been variously estimated as ranging from 7,500 to 12,800 milligrams per kilogram of body weight. Technical piperonyl butoxide with 80 per cent of the pure substance was applied to the eyes and skin and administered by stomach tube to rats, rabbits, cats, and dogs by Sarles, Dove and Moore (2) with results indicating that the substance was not markedly toxic nor were solutions of it irritating to the skin. Sarles and Vandegrift (3) investigated the chronic oral toxicity of piperonyl butoxide by feeding large doses of this substance to rats and dogs. Doses of 10,000 to 25,000 parts per million caused anorexia and wasting. There was no evidence of cumulative effects with moderate dosage, nor of carcinogenic activity. The safe human tolerance for chronic ingestion of piperonyl butoxide was estimated to be 42 parts per million in all the food eaten.

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## THE PROPYL ACETATES

### Characteristics

*n*-Propyl acetate, CH<sub>3</sub>COO·C<sub>3</sub>H<sub>7</sub>, is a clear, colorless liquid which boils at 101.54° C. (1), has a density *D*<sub>20/4</sub> of 0.88286, and an index of refraction *n*<sub>20/D</sub> of 1.38468. At 16° C., 1 part of *n*-propyl acetate is soluble in 60 parts of water. The flash point is 12° C. It is soluble in alcohol and ether.

Isopropyl acetate, CH<sub>3</sub>COOCH(CH<sub>3</sub>)<sub>2</sub>, is also a colorless, aromatic liquid which boils at 88.9° C., freezes at -73.4° C., has a density *D*<sub>25/4</sub> of 0.8690, and an index of refraction *n*<sub>25/D</sub> of 1.3740. It is miscible with most of the common organic solvents, has a mild odor, a flash point of 16° C., and vapor pressure of 47.5 millimeters of mercury at 20° C.

The propyl acetates are formed by reacting the *n*- or isopropyl alcohol with acetic acid in the presence of catalysts.

### Industrial Uses

The propyl acetates find extensive use as solvents for nitrocellulose and a wide range of cellulose derivatives, as well as natural and synthetic resins. They are used in the manufacture of lacquers, plastics, synthetic perfumes, and in organic synthesis. *iso*-Propyl acetate was placed on the market in 1932 as a substitute for ethyl acetate in the lacquer industry. It is somewhat superior to the latter with regard to blushing and flowing properties for it evaporates about 17 per cent more slowly than ethyl acetate. It has a lower tolerance for toluene and produces nitrocellulose solutions of appreciably higher viscosities than ethyl acetate (2).

## Toxicity

Browning (3) states that from animal experiments it appears that *n*-propyl acetate has a moderately irritative effect on mucous membranes only a little stronger than that of ethyl acetate, a narcotic effect rather stronger than that of methyl or ethyl acetate, but a lethal effect less than these two substances. In a long-continued nonnarcotic concentration, *n*-propyl acetate produces respiratory irritation and, according to Flury and Wirth (4), some liver injury. The after-effects are slight with quick recovery from even deep narcosis. With repeated inhalation there is definite habituation. The symptoms noted are sleepiness, fatigue, slight stupefaction, and retarded respiration. The vapors of the esters of organic acids on absorption, and probably to some extent on surface tissues as well, are largely hydrolyzed, with the liberation of the acid and the primary alcohol. Since the acetate can be tolerated in comparatively high concentrations with slight irritation, the presence of the alcohols formed in the body raises the point of chronic poisoning (5). While experimental inhalation of rather high concentrations of the propyl acetates have been shown to produce irritation and narcosis and in certain cases death, no permanent industrial injury has been caused in workmen exposed to these acetates. However, Baldi (6) has found that in man exposure to 20 to 60 milligrams per liter causes within 1 week conjunctival irritation, a feeling of oppression of the chest, and cough. Recovery is prompt with cessation of exposure to the ester. The isopropyl acetate has been shown to have slightly less narcotic potency than the *n*-propyl acetate (7).

## Analysis

On hydrolysis with alkali, the propyl acetates yield propyl or isopropyl alcohol and acetic acid. This reaction can be used to advantage in the determination of the acetates as aerial contaminants, in the absence of acid fumes or other esters by absorbing a large sample in alcohol containing a known amount of standard alkali, refluxing, and back-titrating with standard acid.

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## *n*-PROPYL ALCOHOL

### Characteristics

Normal propyl alcohol, propanol-1,  $\text{CH}_3 \cdot \text{CH}_2\text{CH}_2\text{OH}$ , is a colorless liquid with a strong alcoholic odor. It is miscible with water with which it forms a binary constant boiling mixture (boiling point  $87.72^\circ \text{C.}$ ) containing 71.69 per cent by weight of the alcohol. *n*-Propyl alcohol boils at  $97.15^\circ \text{C.}$ , melts at  $-126^\circ \text{C.}$ , has a density  $d_{25/4}$  of 0.79957, and index of refraction  $n_{20/D}$  of 1.38499. This alcohol, which was discovered by Chancel in 1853 in crude fusel oil, may be obtained from the latter by fractionation. *n*-Propyl alcohol is also obtained in appreciable amount as a by-product in the synthesis of methanol.

### Industrial Uses

*n*-Propyl alcohol is a solvent but is not apparently of great practical importance. It is used as a solvent for nitrocellulose, gums, resins, and cellulose esters, and to some extent as a disinfectant (1).

### Toxicity

Browning (2) concludes that the general toxicity of normal propyl alcohol is slight, that it is somewhat more toxic than isopropyl alcohol if judged by injection into animals but less narcotic when inhaled. Lehmann and Flury (3) found that mice be-



came giddy, showed incoordination, and became prostrated after 1½ to 2 hours in an atmosphere containing 0.3 per cent normal propyl alcohol and were in a state of deep narcosis after 10 hours in a 0.4 per cent atmosphere. However, there were no recognizable after-effects. No ill effects from the use of normal propyl alcohol in industry have been recorded nor has any maximum allowable concentration value been established.

### Analysis

In the absence of other alcohols, as little as 1 milligram of *n*-propyl alcohol may be detected by the xanthate reaction (4). *p*-Nitrophenylacetyl chloride is used for the identification of this alcohol. The ester formed melts at 36.5° C. (5). With furfural in the presence of sulfuric acid, normal propyl alcohol gives a violet color. No quantitative method for the determination of normal propyl alcohol as an aerial contaminant is available. In the absence of other solvents, adsorption of the vapor on activated charcoal or silica gel is suggested.

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## *iso*PROPYL ALCOHOL

### Characteristics

*iso*Propyl alcohol, propanol-2, secondary propyl alcohol,  $(\text{CH}_3)_2\text{CHOH}$ , is a colorless, clear, mobile liquid with a slight odor resembling acetone. It is miscible in water, alcohol, and ether, boils at 82.4° C., melts at -89.5° C., has a density  $d_{20/4}$  of 0.78507, and an index of refraction  $n_{20/D}$  of 1.37927.

Since 1919, it has been made from propylene which is available as a by-product in the cracking of heavy petroleum hydrocarbons. The propylene is dissolved in sulfuric acid and the acid ester so formed is hydrolyzed to yield the corresponding propyl alcohol. *iso*-Propyl alcohol may be salted out from aqueous solution by potassium carbonate or potassium fluoride. On oxidation with chromic acid, *isopropyl* alcohol yields acetone and when treated with iodine in alkaline solution, it rapidly yields iodoform, melting point 119° C. Refluxed with hydrogen iodide, it yields *isopropyl*iodide, boiling point 89° C., and when tested with resorcinol and sulfuric acid, it gives an amber ring.

### Industrial Uses

During the year 1954, 858,682,000 pounds of *isopropyl* alcohol were produced in the United States. Of that produced in 1945, 69.8 per cent was allocated for use in the manufacture of acetone, 3.3 per cent for the manufacture of *isopropyl* acetate, and 25.3 per cent for such technical uses as rubbing alcohol, de-icing and anti-freeze, technical coatings, solvents, cleaners and blends, and such miscellaneous applications as textile processing, drugs, cosmetics, plastics, and resins.

### Toxicity

In general, the physiological properties of *isopropyl* alcohol are somewhat similar to those of ethyl alcohol, the action of significant doses on the sympathetic nervous system being first depressant and later paralytic (1). In three cases of *isopropyl* alcohol intoxication McCord *et al.* (2) found that while its action is very similar to that of ethyl alcohol, coma occurs at lower blood concentrations of *isopropyl* alcohol. However, salivation, retching, and vomiting are somewhat less frequent with ethyl alcohol than with *isopropyl* alcohol. The approximate lethal dose as determined on several species of animals is approximately half that of ethyl alcohol. Delayed toxic effects are not observed and the results of chronic intoxication may be interpreted as argument against the production of a harmful intermediary metabolite. Boughton (3) deter-

mined by long-term rat feeding experiments, and also by external application experiments, that *isopropyl* alcohol is only slightly more toxic than ethyl alcohol when taken internally and that neither produces harmful effects externally. The lethal dose obtained by intravenous injection in animals has been found to be 3.2 grams for *isopropyl* alcohol as against 1.6 grams for *n*-propyl alcohol. Inhalation of the fumes of *n*-propyl alcohol causes some narcosis but no symptoms of after-effects have been found in the exposed animals (4). No cases of industrial poisoning from this substance have been reported. In man, concentrations of 400 parts per million produce mild irritation of the eyes, nose, and throat, and at 800 parts per million the effects are not severe but most individuals find the atmosphere unsuitable for breathing (5).

### Analysis

On warming with iodine and sodium carbonate solution, *isopropyl* alcohol yields iodoform, melting point 119° C. When warmed with concentrated HCl, it yields the chloride, boiling point 36° C. The carbanilate melts at 90° C.; the *p*-nitrobenzyl phthalate at 74° C. *iso*Propyl alcohol may also be identified by the formation of its derivative *iso*propyl 3,5-dinitrobenzoate (melting point 122° C.). With furfural in the presence of sulfuric acid, *isopropyl* alcohol gives a red-violet color. However, the latter test is not specific and may be confused by the response of other alcohols when present. *iso*Propyl alcohol can be detected by the orange color produced by guaiacoldialdehyde (4-hydroxy-5-methoxyisophthalaldehyde) test (6). When present in sufficient amount, *isopropyl* alcohol may be determined quantitatively by the iodine titration method (7).

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## *iso*PROPYL BENZENE

### Characteristics

*iso*Propyl benzene, cumene,  $C_6H_5CH(CH_3)_2$ , boils at 152.5 C., melts at -96.2° C., has a density  $D_{20/4}$  of 0.8633, and an index of refraction of  $n_{20/D}$  of 1.49157. It is a colorless liquid, insoluble in water but soluble in alcohol, carbon tetrachloride, ether, and benzene. *iso*Propyl benzene, one of the higher homologues of the benzene series, is one of fourteen aromatics isolated by the National Bureau of Standards from the gasoline fraction of petroleum. These are all alkyl derivatives of benzene. On oxidation with dilute nitric or chromic acids, *isopropyl* benzene yields benzoic acid. Furthermore, on nitration with subsequent reduction with nascent hydrogen and acetylation, it yields 4-acetylamino-1-*isopropyl* benzene, which crystallizes in glistening flakes from hot water or alcohol and has a melting point of 106° C. *iso*Propyl benzene can be prepared synthetically from either *n*-propyl bromide or *isopropyl* bromide, both of which yield *isopropyl* benzene with benzene in the presence of aluminum chloride. Usually, however, it is obtained by fractionating petroleum.

### Industrial Uses

*iso*Propyl benzene has become an important constituent of high octane aviation fuel which is now produced in quantity. It has, however, other important uses. Higher yields of styrene are obtained by cracking *isopropyl* benzene than from the dehydrogenation of ethylbenzene, but demands for *isopropyl* benzene in high octane gasoline have precluded its use for that purpose (1). It is commonly used as a solvent and in organic synthesis.



## Toxicity

The acute effects of cumene vapors in mice as investigated by Werner and his associates (2) show that both pure cumene and the cumene fraction of petroleum have a potent narcotic action characterized by a slow induction period and long duration. It is depressant to the central nervous system and the minimal lethal concentration for mice was found by these investigators to be 2,000 parts per million. Although the toxic effects develop slowly, they are produced by relatively low concentrations as shown by the LD<sub>50</sub> concentration for cumene, toluene, and benzene in milligrams per liter which are respectively: 10.0, 19.9, and 33.1. However, as a potential industrial hazard when the volatility of the homologues is considered, acute hazards from cumene would be comparatively low or at least they could be controlled with less difficulty than hazards from benzene or toluene under ordinary conditions of temperature and pressure. The long duration of action of cumene, as indicated by a slow rate of elimination, suggests that precautions against possible cumulative effects be considered. The toxicology of *isopropyl* benzene was studied by Fabre and his associates (3) as a possible replacement for benzene as an industrial solvent. In general *isopropyl* benzene appears to be more toxic to the rat than benzene or toluene. Chemical examination of the tissues of exposed rats and rabbits showed that *isopropyl* benzene is localized in the bone marrow, the cerebellum, the spleen, and the adrenals. Histological examination of the tissues showed a slight passive congestion of the liver, lung, spleen, and adrenals.

## Analysis

While *isopropyl* benzene can be determined when mixed with air in concentrations of several milligrams per liter by means of an interferometer, lower concentrations are more difficult to measure. Silica gel or activated charcoal adsorption tubes can be used for this purpose. Known volumes of air can also be drawn through a benzene detector properly calibrated for *isopropyl* benzene and its hydrocarbon content thus be determined. Fabre (3) has devised a photometric

method for the determination of *isopropyl* benzene in biological material based on the color reaction with methyl ethyl ketone in an alkaline medium after removal from the tissues and subsequent nitration.

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## *iso*PROPYL ETHER

### Characteristics

*iso*Propyl ether, diisopropyl ether, (CH<sub>3</sub>)<sub>2</sub>CHOCH(CH<sub>3</sub>)<sub>2</sub>, is a colorless liquid of ethereal odor which boils at 67.5° C., melts at -60° C., has a density *D*<sub>20/20</sub> of 0.7247, and a refractive index *n*<sub>23/D</sub> of 1.3678. It is miscible with most organic solvents but is only slightly soluble in water (0.2 per cent). In many of its properties, it is similar to ethyl ether but it has a higher boiling point, evaporates more slowly, and is less soluble in water. Diisopropyl ether is derived as a by-product in the production of *isopropyl* alcohol from the propylene fraction of cracked gasoline by means of sulfuric acid and is also obtainable in a yield of about 50 per cent by the action of sulfuric acid on *isopropyl* alcohol.

### Industrial Uses

The value of diisopropyl ether in the war program is shown by its increase in production—5,349,000 pounds in 1942 which increased to 10,489,000 pounds in 1943. Production had dropped to 3,267,000 pounds in 1954. Diisopropyl ether is of value in the blending of aviation motor fuel because of its high anti-knock rating. In formulating high-octane gasolines, it is said that an anti-knock rating of 100 can be obtained when 40 per cent of *isopropyl* ether is blended with ordinary gasoline. A saving of fuel of 15 per cent and a gain in power of 30

per cent is thus claimed. Diisopropyl ether is used in the extraction of acetic acid from its aqueous solution and as a solvent in the dewaxing of oils and deoiling of waxes. It is also used in rubber cements and as a varnish remover.

### Toxicity

Machle and his associates (1) studied the physiologic response to isopropyl ether following oral administration, as well as the inhalation of isopropyl ether vapor in various concentrations. The ingestion of isopropyl ether causes a rapid, intense intoxication similar to that of diethyl ether. Failure of respiration caused by its depressant action was the cause of early death from this substance, while one late death resulted from irritation of the intestinal tract from this material. The concentration of 6 per cent of diethyl ether by volume was rapidly fatal to several species of animals, while 3 per cent caused no deaths but produced a light, incomplete form of anesthesia. One per cent isopropyl ether vapor in air caused mild intoxication in a monkey on inhalation but had no effect on rabbits or guinea pigs. By volume, 0.1 per cent and 0.03 per cent isopropyl ether did not noticeably affect rabbits and monkeys exposed for 20 periods of either 2 hours or 3 hours in duration. Although no characteristic pathological changes were found in animals exposed to 3 per cent isopropyl ether which lived for some weeks after exposure, animals exposed to fatal concentrations showed specific pathological lesions. No ill effects were noted following the application of isopropyl ether to the skin of rabbits.

### Analysis

No general method has been devised for the analysis of air samples containing low concentrations of diisopropyl ether, such as found in the atmosphere of work shops and factories. The concentrations of diisopropyl ether investigated by Machle and his associates were, however, satisfactorily determined by means of the Zeiss interferometer and also by a slow combustion method. Samples were also analyzed by a chemical method utilizing the oxidation of diisopropyl

ether by means of standard potassium dichromate. This method was satisfactory for the range investigated.

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## PYRIDINE

### Characteristics

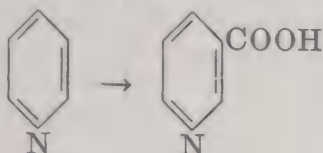
Pyridine,  $C_5H_5N$ ,



is a practically colorless liquid, basic substance having a sharp, penetrating odor. It is an heterocyclic compound in which nitrogen has displaced one carbon and a hydrogen of benzene in the benzene ring. It has a boiling point of  $115^{\circ}C$ ., melting point of  $-42^{\circ}C$ ., density  $d_{15/4}$  0.9893, and index of refraction  $n_{D15}$  1.50919. Pyridine occurs in coal tar, bone oil, and in many vegetable distillation products, including tobacco smoke. It is a very weak base and does not color litmus. It can be extracted together with some of its homologues from the lower-boiling fraction of tar distillates after removal of the tar acids by agitation with sulfuric acid in which they dissolve. Pyridine may be prepared in the pure state from the pyridine-carboxylic acids by distillation with lime. Pyridine is soluble in water and in alcohol and ether. Certain pyridine derivatives have been proposed for use as insecticides, such as benzylpyridine and  $\alpha$ -*p*-tolylpyrrolidine. However, the toxicity of these substances has been found to be low and far less than that of nicotine (1). Certain homologues of pyridine having the general formula  $C_nH_{2n-5}N$ , such as the piccolines, lutidines, collidines, and parvolines, are of minor industrial importance and are therefore of very little industrial toxicological interest. Pyridine is an important starting



material for the synthesis of nicotinic acid



which is now widely recognized as an accessory dietary factor in the disease known as pellagra.

### Industrial Uses

During 1945, 480,676 gallons of refined pyridine were produced as a coke oven by-product in the United States. Somewhat more than 42 per cent of the purified pyridine was used in the manufacture of vitamins, 21.8 per cent for sulfa drugs, 12.7 per cent in the rubber industry, and 6.9 per cent for water repellents. Production amounted to 884,000 pounds in 1954. Pyridine is also used in the manufacture of other medicinals, disinfectants, and dyestuffs, and as a denaturant for alcohol, as well as a paint and rubber solvent.

### Toxicity

The immediate effects of inhalation of pyridine in man are flushing of the face, quickening of the pulse and respiration, temporal headache, tendency to giddiness, nausea, vomiting, and nervousness. After giving pyridine to five patients with epilepsy, Pollock and his associates (2) report that two patients receiving 30 to 40 minims a day for periods up to a month later showed marked toxic effects. In both instances, the effects were those of hepato-renal disease. Death followed in one case; the other case recovered. Meyer (3) describes a case of industrial exposure to pyridine of 13 years' duration, following which the victim showed signs of nervousness, insomnia, giddiness, pain, weakness of the limbs. These signs and symptoms were followed by sudden anuria owing to paralysis of the bladder. Treatment with thiamin produced considerable improvement and Meyer considers that pyridine possibly acts as an anti-vitamin agent.

While pyridine has a powerful drying action on the skin and has been stated to cause dermatitis (4), its toxicity is not very

great. In fact, a 10 per cent solution has been used medicinally by atomizer application for the treatment of asthma and bronchitis. The fumes are irritating to mucous surfaces causing eye and nasal irritation and coughing. When ingested, it affects the central nervous system and tends to produce dyspnea and shallow respiration. Large doses act as a heart poison, while smaller doses stimulate the bone marrow to increased production of blood platelets. The nauseating odor of pyridine probably acts as a sufficient warning agent where workers are exposed to the fumes of this material.

### Analysis

Pyridine readily combines with a number of substances useful for its identification. The picrate melts at 167° C.; the methiodide at 117 °C.; and the ethiodide at 90 °C. With chloroacetic acid, pyridine forms an addition compound having a melting point of 202° C. With 2,4-dinitrochlorobenzene, pyridine gives a purple color on the addition of dilute sodium hydroxide solution. Pyridine forms insoluble coordination complexes with the thiocyanates of a number of metals, such as copper, zinc, cobalt, and manganese. The copper-thiocyanate-pyridine complex is soluble in chloroform, to which it imparts a green color. As an aerial contaminant, pyridine may (in the absence of interfering substances) be determined by drawing a known volume of the air through a measured amount of standardized nonvolatile acid, such as sulfuric acid, in a fritted glass bubbler and back-titrating with standardized alkali. According to Hofmann (5), as little as 0.01 milligram of pyridine per liter of air can be determined by absorbing the pyridine from a 10-liter air sample in 50 to 100 milliliters of normal sulfuric acid and determining the absorption by spectral analysis at 2,550 Angstrom units. Ammonia does not interfere.

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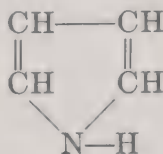
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## PYRROLE

### Characteristics

Pyrrole, divinylenimine, imidole, azole,



is a colorless liquid with an odor characteristic of chloroform. Its boiling point is 130 to 131° C. at 761 millimeters, density  $d_{20/4}$  0.9691 and index of refraction  $n_{20/D}$  1.5085. It is readily soluble in alcohol and in ether and is soluble in water to the extent of 8 grams per 100 cubic centimeters of water at 25° C. Pyrrole is found in coal tar, bone oil, and in the distillate from bituminous shales. It is a very weak base and in fact exhibits a somewhat weakly acidic character in that it forms metallic salts, the imino hydrogen being replaced by potassium when metallic potassium is dissolved in pyrrole or when pyrrole is heated with solid potassium hydroxide, the potassium salt separating out as a crystalline mass. Pyrrole is a very reactive substance and a number of unusual compounds are obtainable by condensation, substitution, or ring expansion reactions. In many respects it exhibits aromatic properties but behaves more like phenol than like benzene and does not increase the output of ethereal sulfates when administered to animals. Strong acids resinify it rapidly. In dilute acids it dissolves slowly and the solution when warmed precipitates an amorphous powder of varying composition, called pyrrole red, with some liberation of ammonia.

### Uses

While pyrrole has practically no technical application of itself, it is a valuable chemical

intermediate, particularly in the manufacture of drugs. For instance, its iodo derivative,  $\text{C}_4\text{I}_4\text{NH}$ , a yellow solid formed by the reaction of pyrrole with iodine and an alkali, is an important antiseptic, acting much like iodoform, but has the advantage of being odorless.

### Toxicity

The physiological response to pyrrole is not remarkable. It causes hypothermia in rabbits (1), the minimum antipyretic dose being 0.0005 gram mole per kilogram of body weight. Death following large doses is accompanied by acute emphysema and pulmonary stasis. Hemorrhagic engorgement of the liver is occasionally seen. According to Rabbeno (2) pure pyrrole does not show the properties of a true anesthetic. Large doses paralyze frogs and weaken the response of the central nervous system in the mouse without raising the excitability of the motor cells. Small doses in the rabbit first stimulate and then paralyze the entire central nervous system, while large doses produce rigidity of the extensor muscles (3). There appears to be some confusion concerning the metabolites formed following the administration of pyrrole. According to Shimizu (4) the injection of an aqueous suspension of pyrrole into dogs is followed by its elimination in the urine as methylpyridine. However the transformations in the body and the excretion products in the urine are somewhat in question. Novello (5), for instance, found that pyrrole in rabbits is excreted in the urine partly as urea and partly unchanged, while Kusui (6) states that no free base could be isolated from the urine following subcutaneous injection. Pyrrole appears to accelerate the oxidation of amines and certain non-natural isomers of the amino acids (7). The intraperitoneal administration of pyrrole in dogs produces epileptic seizures finally leading to death (8). This rather severe type of administration produced injury to the liver which could be demonstrated histologically and the seizures were produced only when the pyrrole was absorbed via the portal system. No cases of intoxication or disability have been reported with reference to pyrrole following



industrial exposure to its vapor, or as the result of skin contact, and there is nothing based upon previous experience to indicate that ordinary exposure to pyrrole would prove especially hazardous.

### Analysis

Pyrrole develops a fiery red color (whence its name) in a pine splint moistened with hydrochloric acid. Salkowski's colorimetric method of analysis (9) is based upon the color pyrrole develops with *p*-dimethylaminobenzaldehyde. More recently Guest and McFarlane (10) have developed a method for the determination of small amounts of pyrrole in biological material in which the indigo-blue color pyrrole gives with isatin is utilized for colorimetric comparison with known amounts of pyrrole.

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## QUINONE AND HYDROQUINONE

### Characteristics

Quinone, *p*-benzoquinone,



is a crystalline solid with a peculiar charac-

teristic irritating odor suggesting chlorine. It melts at 115.7° C., sublimes easily, has a specific gravity of 1.307 to 1.318 at 20° C., and at 5.3° C. has a vapor pressure of  $1.52 \times 10^{-2}$  millimeters of mercury. It is not very soluble in water, but dissolves in alcohol and ether and is volatile in steam. Quinone is unstable in neutral or alkaline aqueous solution. The decomposition is photosensitive, occurring much more readily when the solution is exposed to light. Quinone is prepared from aniline which, on treatment with potassium dichromate and sulfuric acid, is oxidized through various oxidative stages to quinone.

Hydroquinone, quinol, hydrochinone, 1,4-dihydroxybenzene,  $C_6H_4(OH)_2$ , is crystallized from water in the form of white hexagonal prisms. It has a specific gravity of 1.358 at 20° C. and a boiling point of 286° C. The melting point of the purified product is 171° C. and of the commercial product, 168 to 169° C. Hydroquinone is readily soluble in alcohol and ether and soluble in water to the extent of 73 grams per liter of water at 25° C. It is readily oxidized to quinone by nitric acid, the halogens, and persulfates, and in alkaline solution by oxygen. It is oxidized by Fehling's solution in the absence of air and is an inhibitor of the oxidation of a number of substances, such as aldehydes and sulfite solutions. Silver salts are rapidly reduced by it even at ordinary temperature. Hydroquinone occurs in many plants as the glucoside arbutin and is made synthetically by the reduction of quinone.

### Industrial Uses

Quinone is an intermediate in the manufacture of hydroquinone and dyes and is used in tanning (quinone leather). Hydroquinone is extensively used as a photographic developer and as a dye intermediate, and is the base for an increasing number of chemical syntheses. It is an antioxidant and stabilizing agent for preventing deterioration of fats, oils, and resin monomers.

### Toxicity

Sterner, Oglesby, and Anderson (1) summarize the clinical findings from some 50 cases of eye injury occurring in a group of

workmen exposed to quinone vapor and hydroquinone dust in the manufacture of hydroquinone. Before the recognition of corneal injury (1940), the accepted criterion for regulating the concentration of quinone vapor in the workroom was the discomfort of the workman as judged by signs and symptoms of continued eye irritation—conjunctivitis, photophobia, moderate lacrimation, and burning sensation. Later it was found that workmen in this industry developed corneal injuries of two types: a typical superficial greenish-brown stain or grayish-white opacities varying in size and involving all the layers of the cornea. In a few cases there has been an appreciable loss of vision. The eye stain is probably an end product of the oxidation of quinone to hydroxyquinone and the subsequent polymerization of this material. In the pure state, hydroxyquinone has a yellow color but the polymer is a brownish to black relatively stable material. The corneal opacities probably are due to the precipitation of corneal protein or a “scarring” effect and develop gradually over a period of years. Repeated physical examination of these workmen has led to the conclusion that exposure to quinone-hydroquinone of the order sufficient to produce eye injuries is not productive of systemic effects. The odor of quinone becomes perceptible at or just above 0.1 part per million; is definite in the region above 0.15 parts per million; irritating at 0.5 parts per million; and markedly irritating at 3.0 parts per million. A value of 0.1 parts per million was selected by Oglesby and associates (2) as a tentative maximum allowable concentration for quinone vapor. Hydroquinone dust, due to its oxidation to quinone in the presence of moisture, may be a considerable source of atmospheric quinone contamination. Since these investigators found the relative contribution of quinone vapor or hydroquinone dust to the production of the lesions difficult to assess, they arbitrarily selected a maximum allowable concentration value of 2 to 3 milligrams per cubic meter as a practical working level for hydroquinone dust.

### Analysis

In the analytical procedure for quinone as an aerial contaminant used by Oglesby, Sterner, and Anderson (2), the air samples were taken in the midjet impinger with isopropyl alcohol as the absorbing agent. The color developed with phloroglucinol in potassium hydroxide was compared with standards at 520 millimicrons using the Evelyn colorimeter. The reproducibility is good between 0.1 and 2 micrograms and the range is satisfactory for actual factory air measurements.

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## STYRENE MONOMER

### Characteristics

Styrene, vinylbenzene, phenylethylene,



is a highly refractive, oily, colorless to yellowish liquid, having an aromatic odor reminiscent of both benzene and naphthalene. Its melting point is  $-33^\circ\text{C}$ ., density  $d_{20/4}$  0.9090, and index of refraction  $n_{20/D}$  1.5463. It has a vapor pressure of 4.3 millimeters of mercury at  $15^\circ\text{C}$ . Styrene boils at 145 to  $145.8^\circ\text{C}$ . The limits of inflammability of styrene by volume in dry air are 1.1 per cent at a temperature of  $29.3^\circ\text{C}$ . and 6.1 per cent at a temperature of  $65.2^\circ\text{C}$ . (1). Styrene polymerizes to a glassy mass of “metastyrene” on standing, a change which is greatly accelerated by light, heat, or a drop of sulfuric acid. When styrene is added to an acetic acid suspension of sodium thiocyanate and anhydrous copper sulfate, it yields styrene dithiocyanate, which crystallizes from alcohol as white crystals having a melting point of  $103^\circ\text{C}$ . On oxidation with chromic acid, it yields benzoic acid



and on hydrogenation with platinum-black catalyst it yields ethylcyclohexane. Coal tar contains a small per cent of styrene. Styrene is one of the reactive unsaturated materials present in coal gas which are responsible for the troublesome deposition of gums in gas mains and meters. Commercially, styrene is produced from ethylbenzene, for which latter substance a variety of commercial processes of production exist. Ethylbenzene is catalytically dehydrogenated to styrene at high temperatures. Yields of 50 to 80 per cent are thus obtained. Higher yields of styrene are obtained by cracking isopropyl benzene. Styrene is also produced by cracking crude oil.

### Industrial Uses

Styrene has attained a position of considerable importance in industry. Production in the United States in 1953 amounted to 798,433,000 pounds. The increased manufacture of Buna S rubber, as well as polystyrene plastics, has been principally responsible for the increased utilization of this substance. The copolymerization of styrene and butadiene forms a rubbery substance known as Buna S, which is used chiefly for the manufacture of tires and other objects usually manufactured from natural rubber. The increased use of polystyrene plastics is attributable to the very favorable properties of polystyrene. It is one of the lightest of the plastics, has outstanding water resistance, and, although thermoplastic, it possesses unusually good dimensional stability at room, or slightly higher, temperature. The commercial grades of polystyrene are clear, transparent substances capable of transmitting 90 per cent or better of white light. Polystyrene is an excellent electrical insulator since it has dielectric properties similar to those of fused quartz.

### Toxicity

While styrene does not represent a serious health hazard, an American War Standard maximum allowable concentration value of 400 parts per million was established in 1944 (2). Spencer and his associates (3) exposed rats and guinea pigs to various concentra-

tions of styrene up to the maximum concentration that can be obtained under room conditions. At this concentration, which is approximately 10,000 parts per million, they found that this atmosphere was dangerous in from 30 to 60 minutes. The maximum concentration which animals could tolerate for 60 minutes without serious systemic disturbance was 2,500 parts per million. Slight symptoms were obtained following prolonged exposure at 1,300 to 2,000 parts per million and the first symptoms, such as eye and nose irritation, followed exposure to 650 to 1300 parts per million. According to these investigators, the extreme eye and nose irritation produced in man by a concentration of 1,300 parts per million affords a definite safeguard against acutely hazardous conditions.

### Analysis

In determining the concentration of styrene existing as a contaminant in air, Rowe and his associates (4) have adopted a method of trapping followed by various procedures, either physical or chemical, for quantitative evaluation. Carbon tetrachloride, carbon disulfide, methanol, or ethanol are recommended as trapping fluids depending on which method of analysis is followed. The quantitative determination of styrene dissolved in such solvents may be carried out by either ultra violet absorption or by infra red absorption with satisfactory accuracy. However, the nitration method is also satisfactory and perhaps more generally useful in the average laboratory. Quantities of monomeric styrene up to 5 milligrams were determined with an accuracy of 0.15 milligram in 86 per cent of the 78 analyses made and the largest error in any instance was 0.40 milligram (4).

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## TETRABROMOETHANE

### Characteristics

Tetrabromoethane, acetylene tetrabromide, *sym*-tetrabromoethane, 1,1,2,2-tetrabromomethane,  $\text{CHBr}_2\text{—CHBr}_2$ , is a colorless, somewhat odorous, heavy, very refractive liquid having a density of  $d_{20/4}$  2.964, a boiling point of  $151^\circ\text{C}$ . at 54 millimeters, a melting point of  $-1.0^\circ\text{C}$ ., and an index of refraction of  $n_{20/D}$  1.638. It dissolves in water to the extent of only 0.651 gram per liter at  $30^\circ\text{C}$ . but is completely miscible with alcohol, ether, chloroform, and aniline. Tetrabromoethane is prepared by the interaction of acetylene and bromine. Zinc dust and alcohol convert it to acetylene dibromide, while benzene and aluminum chloride react with it to form anthracene.

### Uses

Tetrabromoethane is used as a solvent and to some extent it is used as a refractive index liquid in microscopy. It is an important heavy liquid for the separation of mineral suites by geologists (1, 2), since it is a heavy liquid, is inexpensive, and is not decomposed by ordinary minerals or even by the sulfide minerals.

### Toxicity

Tetrabromoethane is surprisingly less toxic than one would anticipate from its composition and the behavior of some of its congeners. Formerly rated as rather toxic, Gray (3) found by animal experimentation that it could be classified as moderately toxic when ingested. When the vapor of tetrabromoethane was administered by inhalation the toxicity appeared to be much lower. Compared with  $2\frac{1}{4}$  per cent methyl chloride vapor, exposure to tetrabromoethane-saturated vapor was much less toxic to exposed animals. No accumulative effect

was found for repeated short exposures. Irish and his associates (4) exposed groups of rats, guinea pigs, rabbits, mice and monkeys 7 hours a day, 5 days a week to vapor concentrations of tetrabromoethane of 1 to 5 parts per million for periods of 6 to  $6\frac{1}{2}$  months. The growth of the male guinea pigs was moderately depressed but growth, mortality, and gross pathological examination of the rats, rabbits, mice, and female guinea pigs were without significance. Histopathological examination of the tissues of the rats revealed slight fatty degeneration in the parenchymal cells of the liver and slight cloudy swelling of the convoluted tubules of the kidneys. Repeated exposure to 1 part per million of tetrabromoethane of all types of animals was without adverse effect and no microscopic changes were found in the tissues. One part per million was suggested on the basis of these experiments as an industrial hygiene standard for tetrabromoethane.

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## TETRACHLOROETHANE

### Characteristics

1,1,2,2-Tetrachloroethane, acetylene tetrachloride, symmetrical tetrachloroethane,  $\text{CHCl}_2\cdot\text{CHCl}_2$ , molecular weight 167.86, boiling point  $146.3^\circ\text{C}$ ., melting point  $-43.8^\circ\text{C}$ ., density  $d_{20/4}$  1.60, is a colorless liquid. The vapor pressure at  $20^\circ\text{C}$ . is 11 millimeters of mercury. The refractive index is 1.4918 at  $25^\circ\text{C}$ . It is only slightly soluble in water, dissolving to the extent of 0.869 per cent at  $20^\circ\text{C}$ . However, it is completely miscible with organic solvents. Tetrachloroethane vapor is heavy with reference to air, since its relative density is 5.8. 1,1,2,2-Tetrachloroethane is produced by the addition of two mols of chlorine to acetylene under controlled conditions.



Owing to the fact that there are two isomeric substances having the formula  $C_2H_2Cl_4$ , these are frequently confused. The symmetrical form described above is designated as 1,1,2,2- $CHCl_2 \cdot CHCl_2$ , whereas the asymmetrical one is indicated as 1,1,1,2-tetrachloroethane,  $CCl_3 \cdot CH_2Cl$ . The asymmetrical tetrachloroethane is a colorless liquid having a boiling point of  $129^\circ C$ . and a density of 1.5825. It does not have any extensive industrial use.

### Industrial Uses

In addition to its excellent properties as a solvent, tetrachloroethane has the advantage of a higher boiling point than many solvents in common use. It has proved useful as a solvent for lacquers, resins, and waxes, in paint and varnish removers, as an insecticide, in foam fire extinguishers, and in rubber manufacture. Cellulose acetate dissolved in tetrachloroethane was used during World War I as a waterproof coating for airplane wings. On account of its toxic effects however, this application of tetrachloroethane was greatly restricted and, in fact, forbidden in several countries. The use of tetrachloroethane collodion ("essence d'orient") to impart a nacreous luster to artificial pearls has also been forbidden in several countries. Workers in this industry are exposed to tetrachloroethane not only by inhaling the vapor but also in manipulating the liquid with their hands. Other applications of tetrachloroethane have been made in the artificial silk industry, nonflammable photographic film, and in the manufacture of safety glass.

### Toxicity

Many cases of chronic poisoning by inhalation of the vapor of tetrachloroethane have been reported. Lehmann (1) has shown that tetrachloroethane is the most dangerous of all the chlorinated hydrocarbons, being about four times as toxic as chloroform and nine times as toxic as carbon tetrachloride. Industrial intoxication from tetrachloroethane arises mainly from absorption of this substance through the lungs. Deaths have also been recorded from ingested tetrachloroethane (2). In addition to its defatting action on the skin and accompanying der-

matitis, it has been shown by Schwander (3) that enough tetrachloroethane may be absorbed to be detected in the breath and to produce complete narcosis and death. Tetrachloroethane is largely excreted through the lungs but this occurs slowly and part of the absorbed material is excreted in the urine. As a narcotic poison, it acts more slowly than chloroform but the effects are more lasting. In addition to the narcotic action, tetrachloroethane produces organic damage, especially acute yellow atrophy of the liver. The hepatic form of the disease has been divided into four stages with characteristic symptoms at each stage. In the initial stage there is gastric distress, colic, and vomiting. Jaundice with clay-colored stools and constipation are found in the second stage. Definite toxic symptoms appear in the third stage with uremia, somnolence, delirium, and coma. The fourth stage is characterized by ascites, violent gastrointestinal symptoms, and death. Polyneuritis has occurred with workers handling this substance and may be the direct result of cutaneous absorption, since those in the artificial pearl industry who were exposed to the vapor suffered only from giddiness, while those who handled the liquid developed polyneuritis (4). Chronic poisoning following the inhalation of repeated small doses of tetrachloroethane is manifested by nervous symptoms consisting of tremors, headaches, pain in limbs, numbness of the extremities, loss of knee jerks, and excessive sweating. Blood changes also occur before obvious symptoms can be detected. It has been suggested that an increase of the large mononuclear cells to more than 12 per cent should be regarded with suspicion (5). The maximum allowable concentration for tetrachloroethane vapor in the air of workshops is 5 parts per million.

No investigation has been reported so far with reference to the toxicity of asymmetrical (1,1,1,2-) tetrachloroethane.

### Analysis

As in the case of other halogenated hydrocarbons, the presence of tetrachloroethane vapor in air may be detected by the usual copper flame test and may be qualitatively

evaluated by adsorption on air equilibrated activated charcoal or on silica gel. The combustion apparatus devised by Tebbens (6) may be utilized for its quantitative determination, and Barrett's method (7), or the sulfur lamp combustion method of Elkins, Hobby, and Fuller (8) may be utilized. Analytical separation of the two isomeric tetrachloroethanes and the relative proportion of the two substances present in liquid form may be accomplished by fractional distillation (2). A portable, rugged, and inexpensive combustion apparatus has recently been developed for the rapid estimation of low concentrations of tetrachloroethane in air (9).

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### TETRACHLOROETHYLENE

#### Characteristics

Tetrachloroethylene, perchloroethylene, carbon dichloride, or ethylene tetrachloride,  $\text{Cl}_2\text{C}=\text{CCl}_2$ , is a colorless, noninflammable liquid with a faint ethereal odor. It boils at  $121^\circ\text{C}$ . and solidifies at about  $-22^\circ\text{C}$ . The density  $d_{25/25}$  is 1.610 and the index of refraction is  $n_{20/D}$  1.5018. It is almost insoluble in water, dissolving only to the extent of 0.01 per cent. Its vapor pressure

at  $20^\circ\text{C}$ . is 58.5 millimeters of mercury and its evaporation rate is 28 on the basis of an evaporation rate for ether of 100. Tetrachloroethylene is miscible with alcohol, ether, benzene, and other organic solvents. It is prepared from pentachloroethane by removal of hydrogen chloride.

#### Industrial Uses

Tetrachloroethylene has been extensively used as a dry-cleaning agent, since its introduction in the trade in 1934, and as a degreasing substance in industry. The production of this substance in 1944 in the United States amounted to 75,128,000 pounds. It has minor uses in the printing industry and is used to some extent in organic preparations and in solvent mixtures for cellulose esters and ethers and synthetic rubber. Production in the United States in 1953 amounted to 152,917,000 pounds.

#### Toxicity

Although tetrachloroethylene has been stated to be but slightly toxic (1, 2), it should not be regarded as harmless. It is undoubtedly true that its toxicity is, in general, less than that of carbon tetrachloride (3) and chloroform. However, Barsoun and Saad (4) showed that when administered by subcutaneous injection, tetrachloroethylene proved to be more toxic than carbon tetrachloride. As a narcotic agent, tetrachloroethylene is about 2.8 times as powerful as carbon tetrachloride. In common with other halogenated hydrocarbons, it would be anticipated that tetrachloroethylene would act as a metabolic poison and would have a definite toxic effect on the liver and kidneys. Lamson and his associates (5), however, found no pathological changes, excepting a slight and not abnormal fatty metamorphosis of the liver in animals receiving 0.3 to 25 milliliters per kilogram of body weight. The initial symptoms of large doses are stupor, dizziness, excessive perspiration, nausea, and vomiting. The inhalation effects are much less marked than those produced by oral administration. In spite of the fact that the toxicity of tetrachloroethylene is less than that of carbon tetrachloride and that no



well-authenticated fatalities have occurred in industry in this country, reasonable precaution should be observed in handling the material in quantity where excessive exposure may occur. Morse and Goldgerg (6) in their investigation of degreasing units found 11 degreasing units of the nonventilated, noncondensing type in which the tetrachloroethylene concentration reached 221 parts per million. They made recommendations for the design of these tanks, their operation, and location. Crowley and his associates (7) have more recently surveyed degreasing installations where this solvent is in use and found that tetrachloroethylene in the breathing zone of the operator averaged 180 parts per million while work was being put in and 484 parts per million while work was being removed from the tanks. They recommend for safe operation that this type of tank be used only when equipped with condenser and local exhaust ventilation and that all other generally accepted standards for safe degreaser operation be observed.

### Analysis

The silica gel method of determining atmospheric organic solvent vapors of Cralley and his associates (8) has been applied by Pernell to the analysis of tetrachloroethylene vapor in air (9). Over concentration ranges of 2,200 to 2,500 parts per million, the recovery was somewhat better than 82 per cent. At concentrations of from 97 to 304 parts per million the recovery averaged 93 per cent. Using a modified combustion method, Schayer and Ackerman (10) found that tetrachloroethylene vapor can be determined with an accuracy of 88 to 95 per cent.

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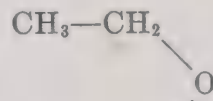
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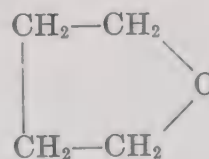
## TETRAHYDROFURAN

### Characteristics

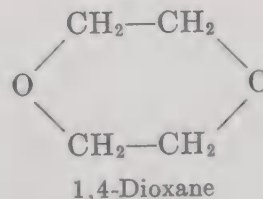
Tetrahydrofuran, tetramethylene oxide, is a colorless, mobile liquid with a neutral reaction. It has a boiling point of 65 to 66° C., a freezing point of -65° C. and a density of  $d_{21/4}$  0.888. Structurally and chemically it is related to diethyl ether and to 1,4-dioxane:



Diethyl ether



Tetrahydrofuran



1,4-Dioxane

### Uses

Tetrahydrofuran is an excellent solvent and is chiefly used in industry as a solvent for resins and in the formulation of lacquers.

## Toxicity

The principal effect of inhalation of tetrahydrofuran is narcosis. According to Lehmann and Flury (1) the inhalation of 3,400 to 60,000 parts per million of tetrahydrofuran vapor by cats, rabbits, rats, and mice over an extended period of time indicated that this substance is narcotic in action and productive of mucous membrane irritation. It was also found to be a skin irritant and damaging to the liver and kidneys. Tetrahydrofuran resembles diethyl ether in several respects. However, narcosis is slower in building up than with ether, and persists somewhat longer. Stoughton and Robbins (2) report that the inhalation of high concentrations of tetrahydrofuran is accompanied by a fall in blood pressure and strong respiratory stimulation. Zapp (3) found that the inhalation of 200 parts per million of tetrahydrofuran by dogs in 6-hour exposures for periods of 3 or 4 weeks produced a fall in pulse pressure but no demonstrable histopathological changes in the principal organs despite an exposure of 9 weeks followed by exposure for an additional 3 weeks at nearly twice this level. In contrast with earlier reports tetrahydrofuran was found not to irritate the skin nor to be a skin sensitizer. Hofmann and Oettel (4) have noted variation in skin effects with different lots of technical tetrahydrofuran and, since peroxide formation readily occurs with this substance, as is the case with diethyl ether, they state that it is possible that the pronounced irritation noted in earlier investigations may have been due to such transformation products rather than to tetrahydrofuran itself.

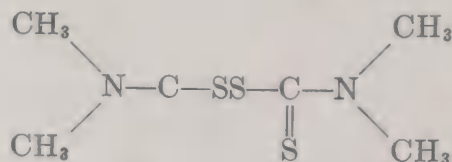
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## TETRAMETHYLTHIURAM DISULFIDE

### Characteristics

Tetramethylthiuram disulfide, bis(dimethylthiocarbamyl disulfide), thirad, thiram,



appears commercially as a white, odorless and tasteless powder which melts at 146 to 148° C. Its density is  $d_{20/4}$  1.29. It is insoluble in water, caustic soda solutions, or gasoline, but is somewhat soluble in alcohol, benzene, and acetone and is very soluble in chloroform and in carbon disulfide. When heated tetramethylthiuram disulfide is decomposed into carbon disulfide and ammonium thiocyanate.

### Uses

Tetramethylthiuram disulfide has been used for a number of years as a vulcanization accelerator in the rubber industry and is efficiently used where heat resistance is essential, as in steam hoses and conveyor belt covers. It is also a fungicide and a valued disinfectant for seeds as well as a pesticide. The extent to which this substance is used commercially is indicated by the production figure of 4,770,000 pounds—the amount manufactured in the United States in 1954.

### Toxicity

The toxicity of tetramethylthiuram disulfide was investigated for the first time by Hanzlik and Irvine (1), who administered the dry powder intragastrically to 16 rabbits and a cat. The minimum fatal dose for rabbits was 0.35 gram per kilogram of body weight; that for a cat was 0.23 gram per kilogram. The symptoms produced were characterized by a gradual depression with ataxia, fall of body temperature, slowed respiration and pulse with, finally, paralysis of the higher functions and death. Cyanosis was pronounced. The effects of subfatal



doses were frequently not observed until the end of the second day. Tetramethylthiuram disulfide was found to be about 10 times as toxic as tetraethylthiuram disulfide (also known as Antabuse and which, more lately, has attained some popular interest as a proposed remedy for alcoholism). The delayed effects following the administration of tetramethylthiuram disulfide appear to be due to the slow rate of absorption of this substance owing to its insolubility in water, acids, and alkalis. While it is doubtful if a sufficient amount of this substance would be swallowed by workers in its industrial applications to cause systemic poisoning, it does cause irritation of the eyes, nose, throat, and skin and would be harmful if breathed as dust suspended in air, or as a spray or mist. According to Schwartz (2) this substance produces dermatitis only when it is contained in rubber in such quantities that it "blooms" out, or is so loosely incorporated that it is leached out by perspiration. The repellent action of tetramethylthiuram disulfide against the Japanese beetle was found by Tisdale and Flenner (3) to be due to partial paralysis of the forelegs and mouth parts of the insect.

### Analysis

While several methods for the detection and estimation of tetramethylthiuram disulfide in quantity have been proposed, none has been specifically developed for small amounts existing as an atmospheric contaminant. It is possible that the dark-green color which this substance yields with cobalt oleate in benzene (4) could be utilized colorimetrically for this purpose.

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## TETRANITROMETHANE

### Characteristics

Tetranitromethane,  $C(NO_2)_4$ , is a colorless, oily liquid which melts at  $13^\circ C.$ , boils at  $126^\circ C.$ , has a density  $d_{13/4}$  of 1.65; and an index of refraction  $n_{16.9/He}$  of 1.43976. It is freely soluble in ether or alcohol but is insoluble in water. It has a characteristic acrid, pungent, biting odor similar to that of nitrous fumes but is much more irritating. It is formed as an impurity in the manufacture of trinitrotoluene by the nitration of toluene. Since the presence of tetranitromethane is objectionable, trinitrotoluene is purified by treatment with sodium sulfite which destroys the tetranitromethane. Tetranitromethane may be prepared by the interaction of acetic anhydride and nitrogen pentoxide or very concentrated nitric acid. It may also be obtained by warming nitroform,  $CH(NO_2)_3$ , with a mixture of fuming nitric acid and sulfuric acid. It is quite stable and distills without exploding. However, when mixed with other carbon compounds, it explodes violently on ignition. With many unsaturated aliphatic and aromatic compounds, tetranitromethane forms colored addition products varying in tint from yellow to brown-red and it is therefore a useful reagent for detecting double bonds.

### Industrial Uses

Tetranitromethane, since it occurs principally as an impurity in the manufacture of trinitrotoluene, is of toxicological interest from this point of view rather than from its industrial application. Tetranitromethane combines with rubber to form a so-called tetranitromethanate, which has been of some service with reference to study of the group relationships in rubber chemistry. These tetranitromethanates, when prepared at  $0^\circ C.$  are fine powders, insoluble in all the common organic solvents, and are noncrystalline. The tetranitromethanates are of academic rather than commercial interest, however.

### Toxicity

Despite cases of poisoning and deaths which were traced to tetranitromethane oc-

curing as an impurity in trinitrotoluene manufacture during World War I, very little experimental investigation of the toxicity of tetranitromethane was made prior to the study made by Sievers and his associates (1). Also during the first World War, the irritating property of tetranitromethane fumes constituted an industrial nuisance and seriously interfered with the production of trinitrotoluene. According to Sievers, the plants in this country in 1915 introduced an alkaline sulfite wash to remove this unpleasant odor. Koelsch, in 1917 (2), reported a limited number of experiments with cats and these are briefly referred to by Flury and Zernik (3). These experiments indicated that as low a concentration as 10 parts per million of tetranitromethane caused fatal poisoning. Koelsch states that animals exposed to the fumes of TNT containing tetranitromethane were unaffected at room temperature. Sievers, however, found that tetranitromethane fumes are given off from crude TNT containing this impurity in sufficient amount at room temperature to be fatal to cats confined in an exposure chamber. Concentrations of from 3.3 to 25.2 parts per million of air produced marked irritation of mucous membranes of the eyes, mouth, and upper respiratory tract, caused pulmonary edema, mild methemoglobinemia, and probably fatty degeneration of the liver and kidneys. Concentrations of from 0.1 to 0.4 part per million caused mild irritation in cats but no other untoward effects following exposure of 6 hours on 2 consecutive days. In view of the above experimental work with animals and the fatal cases described in trinitrotoluene plants by Fischer (4) and by Koelsch (2), which were found to be due to tetranitromethane, this substance is indubitably very toxic. While the TNT product of today is practically free of tetranitromethane, the crude TNT is still a potential hazard with respect to this by-product. In a study of acute and chronic inhalation poisoning with tetranitromethane Horn (5) found that the principal cause of death of the experimental animals was pneumonia, apparently initiated by the irritant property of tetranitromethane. The pathological changes seen in other organs than the lungs were

probably secondary to the marked lung pathology.

### Analysis

The only method so far available for the determination of tetranitromethane in air is that of Rushing (1, p. 6). In this method, air samples were drawn through ethanol as the collecting medium in midget impingers, neutralized with pyridine to a pH of about 6, and treated with alcoholic benzidine solution. Suitable aliquots thus prepared may be compared with known standards in Nessler tubes or the color comparison may be made with a spectrophotometer at 400 millimicrons. Nitrous and nitric acids and their reaction products with alcohol do not seriously interfere. A somewhat modified form of Rushing's method has been employed by Vouk and Weber (6) for the determination of small amounts of tetranitromethane in air.

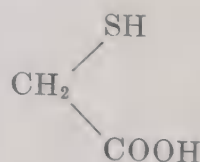
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## THIOGLYCOLLIC ACID

### Characteristics

Thioglycollic acid, thioglycolic acid, mercaptoacetic acid,



is a colorless liquid with a pronounced and



disagreeable odor. Its boiling point is 123° C. at 29 millimeters; freezing point -16.5° C.; and density  $d_{20}^{20}$  1.325. It is miscible with water, alcohol, ether, and many organic solvents. Thioglycollic acid is prepared by reacting monochloroacetic acid with potassium sulfhydrate, or by heating thiohydantoin with alkali.

### Uses

The sodium and ammonium salts of thioglycollic acid are used for cold waving. Thioglycollic acid is also used as an analytical reagent for the colorimetric determination of various metals. Production of thioglycollic acid salts in the United States in 1953 amounted to 1,414,000 pounds.

### Toxicity

While no reports are available of workers being affected in plants for the manufacture of thioglycollic acid, this substance has attained some hygienic importance in its application to cold waving. Both operators and patrons have been affected by the application of salts of thioglycollic acid and numerous cases of skin irritation (1, 2) and even loss of hair (3) have been reported. However, Frenkiel (4) states that irritation is due to impurities introduced by careless manufacture—such as too great alkalinity of the salts or the presence of sodium hydrosulfide. Schulte and Weisskopf (5) patch-tested a number of individuals with solutions containing up to 7.5% of ammonium thioglycollate having pH values of from 7 to 10.4 with negative results. According to these investigators (6), buffered alkaline solutions of pH > 10 attack the peptide linkages of the keratin fibers. This action increases with increasing pH and time of application. Cohen (2) states that thioglycollate preparations should not be used on anemic individuals, nor in cases of liver disease. Van der Burg (7) reports a case of an operator who complained of poor appetite, discomfort and dizziness, irritation of the eyes and lameness of the arms. The reaction in this case was in part due to hypersensitivity.

### Analysis

Thioglycollic acid is an excellent colorimetric reagent for the detection and estima-

tion of ferric iron, with which it gives an indigo-blue color. The color in alkaline solution tends to fade, but is readily restored by shaking with air. With small amounts of iron fading does not occur for 30 minutes. Doubtless the reverse procedure using ferric iron as the reagent could be adapted to the determination of small amounts of thioglycollic acid as an atmospheric contaminant.

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## TOLUENE

### Characteristics

Toluene, toluol, methylbenzene, phenylmethane,  $C_6H_5CH_3$ , a homologue of benzene, melting point -95.1° C., boiling point 110.7° C., density  $d_{25/4}$  0.861, index of refraction  $n_{20/D}$  1.49685, flash point 6.5° C., is a colorless liquid with a characteristic odor. The vapor pressure of toluene is 36.7 millimeters of mercury at 30° C. It burns with a smoky luminous flame, is soluble in water to the extent of 0.19 part per hundred, and is completely soluble in organic solvents. Toluene is present in coal tar and is found together with benzene in the first fraction on fractionally distilling the tar. It is also obtainable from balsam tolu and other resins. A tremendous expansion of toluene production occurred during World War II when the demand for TNT was great. This increase in production was made possible by the development of a catalytic process known as

"hydroforming" in the petroleum industry in 1941. In this process, heavy naphtha fractions undergo an hydrogenation, dehydrogenation, and aromatization process giving a high yield of aromatics. Toluene closely resembles benzene in its properties in forming nitro and other derivatives. Toluene dissolves in methyl nitrite even at  $-20^{\circ}\text{C}$ . and in aniline at  $+20^{\circ}\text{C}$ . When oxidized with dilute potassium permanganate, it yields benzoic acid. Nitration produces 2,4-dinitrotoluene, melting point  $70$  to  $71^{\circ}\text{C}$ . With picric acid, toluene forms a picrate consisting of light yellow flakes, melting point  $88.2^{\circ}\text{C}$ .

### Industrial Uses

Toluene is used extensively as a solvent in the synthetic rubber, paint, and lacquer industries, and in the manufacture of trinitrotoluene in the explosives industry. Toluene constitutes from 2 to 10 per cent of commercial benzene. The total production in the United States in 1945 was 150,041,585 gallons (1). In 1954 production was 159,185,000 gallons.

### Toxicity

There is no complete agreement with reference to the relative toxicity of toluene and benzene, probably owing to differences in the methods of investigation which have been used to evaluate the toxicities of these two substances. It is occasionally asserted that there is a difference in toxicity between toluene and benzene because of the difference in volatility. This belief is doubtless due to confusion of the terms concentration and vapor tension. Industrial exposure is chiefly related to inhalation of toluene vapor which causes a progressive depressant action on the central nervous system and the bone marrow. In addition to its narcotic action, toluene is a pronounced irritant to mucous surfaces. The symptoms of toluene poisoning vary with the degree of exposure (2). Severe exposure causes headaches, dizziness, anorexia, palpitation, weakness, and lack of coordination. A pronounced drop in red cell count occurs. Biopsy of sternal bone marrow reveals partial destruction of the blood forming elements. Toluene is oxidized in the body

to benzoic acid and this in turn (3) combines with glycine in the kidney to form hippuric acid which is excreted in the urine. While it should be kept in mind that commercial toluene contains up to 15 per cent of benzene (4), sufficient investigation has been made of pure toluene to establish its toxicity. According to Wilson (2), who studied 1,000 workmen exposed to various concentrations of toluene for varying periods of time, concentrations above 200 parts per million may cause symptoms attributable to intoxication of the central nervous system, while with concentrations above 500 parts per million, depression of the bone marrow may occur. Greenburg and his associates studied 106 painters exposed to the inhalation of toluene of between 100 and 1,100 parts per million for periods of time ranging from 2 weeks to more than 5 years. They found that industrial exposure to toluene resulted in enlargement of the liver, macrocytosis, moderately decreased levels of erythrocyte counts, and absolute lymphocytosis. It did not result in leukopenia. Early chronic toluene intoxication in man is best evidenced by hepatomegalia and macrocytosis (5). A study of the mechanism of toluene intoxication by Srbova and Teisinger (6) has shown that 16 per cent of the inhaled vapor is excreted by the lungs during the desaturation period. The retained toluene is practically entirely converted to benzoic acid and eliminated within 24 hours. The largest part of the benzoic acid derived from the toluene is excreted as hippuric acid; only 10 to 20 per cent is excreted as a glucuronide.

### Analysis

Toluene may be detected by absorption of the vapor in concentrated sulfuric acid containing formaldehyde. The orange-brown color produced is more or less proportional to the amount of toluene contaminant in the air. However, this method is not specific since coal tar naphthas and benzene also yield a similar color. When toluene, dissolved in concentrated sulfuric acid, is treated with several drops of benzal chloride, it gives a characteristic light yellow color. A microcolorimetric method for the determination of toluene proposed by Yant and



his associates depends on nitration with fuming nitric acid (7). On neutralization and extraction with butanone followed by treatment with potassium hydroxide, a reddish-blue color develops, the intensity of which is proportional to the amount of toluene nitrated. By using this method, together with a similar method developed by the same authors for benzene, benzene and toluene can be estimated independently in mixtures of the two. Fabre, Truhaut, and Peron (8) have developed a photometric method which permits benzene and toluene to be determined separately in mixed solvents and in air.

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### TOLUIDINE

#### Characteristics

Toluidine  $\text{CH}_3\text{C}_6\text{H}_4\text{NH}_2$  exists in the three isomeric forms, i.e., *o*-, *m*-, and *p*-toluidine. These are prepared by the reduction of the three corresponding nitrotoluenes. *m*-Toluidine can also be prepared by reduction of *m*-nitrobenzal chloride which is obtained

from *m*-nitrobenzaldehyde. The *o*- and *p*-toluidines are separated by treating a mixture of the bases with less sulfuric acid than is required for neutralization, followed by distillation. Since the *p* compound is the strongest base, it remains as the sulfate. The toluidines may be separated also by taking advantage of their differences in solubility. *o*-Toluidine is a light yellow liquid boiling at 197° to 200° C., melting at -15.5° C., having a density  $d_{20/20}$  of 1.008, an index of refraction  $n_{20/D}$  of 1.5688, and a flash point of 87° C. *m*-Toluidine is a colorless liquid which boils at 203.4° C., solidifies at about -50° C., has a density  $d_{25/25}$  of 0.990, and index of refraction  $n_{22/D}$  of 1.5711. *p*-Toluidine is a solid occurring as white lustrous plates or leaflets. It melts at 44° to 45° C., boils at 200 to 201° C., has a density  $d_{20/4}$  of 1.046, and an index of refraction  $n_{59/D}$  of 1.5532. The solubility of *o*-toluidine in water is 1 part in 70 volumes and of the *p*-toluidine, 1 part in 135 volumes, while *m*-toluidine is but very slightly soluble in water. All three isomers are soluble in alcohol, ether, or dilute acids. When dissolved in sulfuric acid, *o*-toluidine gives a blue color with potassium dichromate changing to purple on dilution. *m*-Toluidine gives a yellow-brown color and *p*-toluidine a yellow color only under similar conditions. With bromine water, *o*-toluidine gives the dibromo derivative, m.p. 50° C.; *p*-toluidine gives a dibromo derivative of melting point 73° C. The acetyl derivative of *o*-toluidine melts at 112° C., of *m*-toluidine at 65° C., and of *p*-toluidine 148° C., while the melting points of the benzoyl derivatives are respectively *o*-toluidine 143° C., *m*-toluidine 125° C., and *p*-toluidine 158° C. The azo- $\beta$ -naphthol derivatives have the following melting points, respectively: that of *o*-Toluidine 128° C., *m*-toluidine 140° C., and *p*-toluidine 130° C. *o*-Toluidine, like aniline, gives a violet color with bleaching powder in aqueous solution following the addition of hydrochloric acid, but *p*-toluidine does not. Ferric chloride precipitates a blue substance known as toluidine blue from a solution of *o*-toluidine in hydrochloric acid. With *n*-butyl chloride, *p*-toluidine gives mono- and di-butyl-toluidines, but *o*-toluidine gives only a mono derivative.

## Industrial Uses

The quantity of *p*-toluidine marketed in the United States for the year 1944 amounted to 1,019,000 pounds. Production figures for the *o*- and *m*-toluidines are not available at this time. Except for a few special uses, such as the use of the mixed toluidines in vulcanizing operations in the rubber industry, as a constituent of flotation oil in the metallurgical industry, as a base for plastics and molding composition, these substances find but little direct application. The toluidines are important chemical substances as starting material for synthetic products, however, such as saccharin and other pharmaceuticals, synthetic perfumes, dyes, intermediates, and other organic chemicals. A certain amount of toluidine has been applied in the synthetic rubber industry to impart elasticity to synthetic rubber, particularly methyl rubber.

## Toxicity

No very good data exist for the comparative toxicities of *o*-, *m*-, and *p*-toluidines. In general, their toxic behavior is comparable to that of aniline. The most frequent type of exposure in industry is that of inhalation of fumes and vapors with additionally a certain amount of skin contact. It is stated that the *o*- and *m*-toluidines, which are liquid at room temperature, are not so readily absorbed through the skin as is aniline. The symptoms produced by the inhalation of the toluidines are those of headache, weakness, difficulty in breathing, convulsions, cyanosis, and kidney irritation. According to Henderson and Haggard (1), a concentration varying from 6 to 23 parts per million of *o*-toluidine causes slight symptoms after exposure of several hours, while 90 to 140 parts per million is the maximum concentration that can be inhaled for 1 hour without serious disturbance.

## Analysis

While toluidine may be estimated by itself or even in the presence of aniline by the potassium bromide-bromate method (2), this procedure is only useful when applied to the estimation of toluidine in relatively larger samples than ordinarily ob-

tained by air sampling. Aniline in this method is converted to a tribromo derivative while the toluidines yield dibromo derivatives. Identification of the various toluidines is usually accomplished by converting to characteristic derivatives and obtaining their melting or boiling points.

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## TOXAPHENE

### Characteristics

Toxaphene is not a definite chemical compound but is instead a mixture of polychloro bicyclic terpenes with chlorinated camphene. The resulting product contains 67 to 69 per cent of chlorine. It is a yellow, waxy substance with a melting point of 65 to 90° C. and has a pleasant piney odor. While it is insoluble in water it dissolves in a number of organic solvents.

### Uses

Toxaphene is an important agricultural insecticide. It is especially useful in cotton raising as a protective measure against the boll weevil, boll worm, cotton aphid, and cotton fleahopper.

### Toxicity

Toxaphene was found by Lackey (1) to be highly toxic to dogs in doses of 10 milligrams per kilogram of body weight when administered by stomach tube. Death resulted from doses as low as 15 milligrams per kilogram, but other dogs survived doses of 40 milligrams per kilogram. Chronic poisoning studies indicated that there is an accumulative effect. Skin absorption was shown by Lackey (2) to occur both with dogs and with rabbits. When dogs were given lethal doses of toxaphene by mouth Lackey and Weed (3) found that convul-



sions could be controlled and that recovery occurred by adequate dosage of sodium phenobarbital. Garcia *et al.* (4) found that there is considerable variation in the lethal dosage of toxaphene for various species of animals.

Several cases of toxaphene poisoning in man have been reported (5) resulting from accidental ingestion (a fatal case), or from eating vegetables sprayed with toxaphene. Pollock (6) reports a fatal case of poisoning in which a child ingested toxaphene. The acute oral toxicity, *i.e.*, the LD<sub>50</sub> value for toxaphene to the rat is 69 milligrams per kilogram. The toxicity to the rabbit by skin absorption was found by Johnston and Eden (7) to be 1.025 to 1.075 gram per kilogram of body weight.

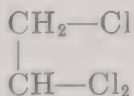
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### TRICHLOROETHANE

#### Characteristics

Trichloroethane exists as two isomers, 1,1,1-trichloroethane and 1,1,2-trichloroethane, and is sometimes incorrectly designated as vinyl trichloride, ethylene chloride, or ethylene trichloride. The 1,1,2-, or  $\beta$  isomer.



is the more important compound industri-

ally. 1,1,1-Trichloroethane or methyl chloroform is a liquid with a boiling point of 74.1° C., a density of  $D_{26/4}$  1.3249, and refractive index of  $n_{21/D}$  1.4376. 1,1,2-Trichloroethane boils at 113.5° C., melts at -36.7° C. has a liquid density of  $D_{20/4}$  1.4406, and an index of refraction of  $n_{20/D}$  1.4715 (1). The vapor pressure of 1,1,1-trichloroethane is 100 millimeters of mercury at 20° C.; that of the 1,1,2-compound is 20 millimeters of mercury at 21.6° C. The density of the vapor of 1,1,2-trichloroethane under 1 atmosphere of pressure and at the boiling point is 4.61 and its solubility in water at 25° C. is 0.44 gram per 100 grams of water (2).  $\beta$ -Trichloroethane is noninflammable. McGovern, in giving the conditions under which it may be used without significant decomposition or corrosion of equipment, states that it may be used in the absence of air and water at temperatures up to 110° C. In contact with water, it hydrolyzes appreciably at its boiling point (113.5° C.). Trichloroethane may be used in the presence of air at ordinary temperatures without danger of decomposition or corrosion.

#### Industrial Uses

1,1,2-Trichloroethane is a solvent for oils, fats, waxes, tar, many natural and synthetic resins, and alkaloids. Its noninflammability and boiling range make it especially suitable for many solvent and degreasing operations. It has distinctive solvent properties for natural and synthetic rubber and is particularly used as a solvent for Thiokol.

#### Toxicity

1,1,2-Trichloroethane is less toxic than 1,1,1-trichloroethane. Both the trichloroethanes have a local irritating effect on the mucous membranes, particularly those of the eyes and nose. In general, these substances have a narcotic effect causing complete narcosis in mice at a concentration of 60 to 65 milligrams per liter of air. According to Lehmann (3), 1,1,1-trichloroethane is four times as toxic as the 1,1,2-compound. Lehmann found serious symptoms of irritation of the nervous system following exposure to these chloro derivatives of ethane. Engorged blood vessels were noted, the liver

was rich in pigment, accompanied by fine and coarse fat deposition, fat was present in the kidneys, and edema and hemorrhage of the lungs occurred. McGovern (2) rates the toxicities of chloroform and 1,1,2-trichloroethane as more pronounced than those of methyl and ethyl chloride, respectively, but these substances were less toxic than pentachloroethane and tetrachloroethane. However, Adams and his associates (4) have obtained more concrete evidence of the toxicity of 1,1,1-trichloroethane as the result of extensive investigation of the effect of this substance on animals exposed to its vapor. Their experiments indicate that trichloroethylene and tetrachloroethylene are much more toxic than 1,1,1-trichloroethane and that the toxicity of the latter is about the same order of magnitude as that of dichloromethane.

### Analysis

The methods of analysis suitable for the determination of carbon tetrachloride may also be applied to the evaluation of the trichloroethanes as aerial contaminants in the absence of other chlorinated hydrocarbons.

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## TRICHLOROETHYLENE

### Characteristics

Trichloroethylene, ethylene trichloride,  $\text{CHCl}=\text{CCl}_2$ , boils at 87° C., solidifies at -88° C., and has a density  $D_{20/4}$  of 1.46. It is miscible with alcohol, ether, and oils but dissolves only very slightly in water (1.18 milliliter per liter or 0.04 per cent at 25° C.). Trichloroethylene is a clear, colorless, noninflammable liquid with a faintly aromatic, sweetish, characteristic odor some-

what resembling chloroform. The vapor pressure at 20° C. is 57.8 millimeters of mercury and at 86.9° C. is 760 millimeters of mercury. Trichloroethylene is classed as noninflammable at ordinary temperatures and moderately flammable at higher temperatures. In the presence of an excess of water or at high temperatures, such as occur in open flames, trichloroethylene may decompose to give hydrochloric acid and other products. Its molecular weight is 131.39 and a concentration of 1 milligram per liter represents 186 parts per million. Trichloroethylene is prepared from *sym*-tetrachloroethane by heating with calcium hydroxide. By autoxidation, it yields dichloroacetyl chloride but a simultaneous decomposition to phosgene, carbon monoxide, and hydrogen chloride also occurs. Owing to its tendency to decompose, trichloroethylene should be protected from light.

### Industrial Uses

Trichloroethylene, because of its solvent action on fats and oils, is used as a thinner for coatings and varnishes and as a solvent for rubber, replacing carbon tetrachloride in many instances. It is used in industry in large quantities as a degreasing agent for metal surfaces previous to coating them with other metals, as a dry-cleaning agent, as well as in the textile and printing industry, in the chemical industry, in gas purification, as an insecticide, a disinfecting agent, and in cleaning films, photographic plates, and optical lenses. In all these processes, trichloroethylene may be used pure or as an addition to other solvents under various proprietary names. Since 1935, it has been used as an inhalation anesthetic similarly to chloroform.

### Toxicity

When used in anesthesia, trichloroethylene permits the use of a higher oxygen percentage, is practically nonirritant, and rarely causes postoperative nausea, but, on the other hand, it does not give satisfactory muscular relaxation. It resembles chloroform but is less potent and less toxic (1). The local irritating effect on the eyes and mucous membranes, the giddiness, excitement, or



confusion are similarly less for equivalent dosages. Severe narcosis is produced only by high concentrations and prolonged exposure. However, numerous cases of trichloroethylene poisoning have been reported in the literature of industrial hygiene. Stüber (2) has recorded 284 cases of trichloroethylene poisoning in German industry of which 202 were acute and 82 chronic. In all there were 26 fatal cases of poisoning. Although Stüber went so far as to state that the liver is never affected, Seifter (3) found that liver injury consisting of liver disfunction, glycogen depletion, and hydropic parenchymatous degeneration developed in dogs exposed to repeated and prolonged inhalation of trichloroethylene vapor. Other signs of intoxication were anemia, loss of weight, nausea, vomiting, lethargy, and diarrhea. However, all signs disappeared in dogs that were removed from exposure. Although liver injury was produced in a short time by exposure to relatively large concentrations, definite liver injury resulted from an exposure of 8 weeks to a concentration of 500 to 750 parts per million 4 to 6 hours daily, 5 days a week. Mogilevskaya (4) states that in addition to its narcotic effect, trichloroethylene specifically attacks the sensory fibers and the visual nerve leading to blindness, causes severe hepatitis and damage to the respiratory organs, which is possibly due to the formation of hydrochloric acid and carbonyl chloride. Barrett and his associates (5) have shown that 5 to 8 per cent of the trichloroethylene absorbed is excreted in the urine as trichloroacetic acid. Powell (6) suggests that routine blood and urine tests for trichloroacetic acid be used to control undue or harmful exposures to trichloroethylene in industry. The animal experiments of Fabre and Truhaut (7) indicate that both trichloroethylene and trichloroacetic acid derived from it are deposited in the endocrine glands, kidneys, brain, blood, and particularly in the spleen and lungs. There is no evidence to indicate that the trichloroacetic acid produced in the metabolism of trichloroethylene is toxic. Ahlmark and Forssman (8) have shown that the extent of exposure to trichloroethylene may be evaluated by determining the trichloroacetic acid content of

the urine. In an examination of 80 workers exposed to an average of 59 parts per million for open tanks and 23 parts per million for closed tanks, Grandjean and his associates (9) found the average ratio of urinary trichloroacetic acid (milligrams per liter) to atmospheric trichloroethylene (in parts per million) to be 3:1. Dermatitis is caused by the defatting action of trichloroethylene upon the skin and results from repeated exposure.

### Analysis

Dudley (10) has described a portable unit for the determination of halogenated hydrocarbons in air which is applicable to the quantitative determination of trichloroethylene. Fujiwara (11) found that when certain chlorinated hydrocarbons were highly diluted in water and treated with sodium hydroxide and pyridine a color is developed on heating. Barrett (12) has developed a procedure based on this method for the determination of trichloroethylene in air. The method yields results accurate to within  $\pm 11$  per cent which is considered quite sufficient for field determinations. Concentrations as low as 20 parts per million may be detected. Further study of this method has been made by Webb, Kay, and Nichol (13), who have developed an improved visual test for its application. Hapgood and Powell (14) have adapted the Fujiwara reaction to the determination of trichloroethylene in blood. In the method developed by Waldman and Krause (15) for determining the trichloroacetic acid content of urine, the acid is decomposed by sodium hydroxide to chloroform and carbon dioxide. In alkaline solution chloroform develops a pink color with pyridine and the depth of color thus obtained is measured colorimetrically. The amount of trichloroacetic acid found is a useful measure of the extent of intoxication by trichloroethylene.

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## TRI-*o*-CRESYL PHOSPHATE

### Characteristics

Tricresyl phosphate,  $(\text{CH}_3\text{C}_6\text{H}_4)_3\text{PO}_4$ , exists in three isomeric forms which possess differences in toxicity. The *o*- and *m*-cresyl phosphates are colorless, practically odorless liquids, which are stable and nonvolatile. The *p* isomer exists in the form of crystalline needles having a melting point of 77–78° C. The tri-*o*-cresyl phosphate has a boiling point of 275 to 280° C. (20 millimeters of mercury), specific gravity of 1.170 to 1.180 at 20° C., and an index of refraction of

1.554 to 1.556 (25° C.). Its volatility is said to be 0.03 per cent at 100° C. While insoluble in water, the phosphates are miscible with all the common solvents and thinners and also with most vegetable oils. Tri-*o*-cresyl phosphate is made by treating cresols with phosphorus oxychloride in the presence of an aluminum catalyst.

### Industrial Uses

Tricresyl phosphate was under the allocation control of the War Production Board from 1942 through 1945. During 1944, a total of 20,715,000 pounds of tricresyl phosphate was distributed as follows: 64.1 per cent for cable impregnation and sheaths; 10 per cent for lacquers; 8.9 per cent for synthetic rubber; 7.5 per cent for textile coatings; 5.2 per cent for cellophane and plastics; 2.4 per cent for direct military uses, and 1.9 per cent for adhesives, synthetic rubber, lubricants, and oil additives. Production in 1953 amounted to 22,109,000 pounds. In the manufacture of plastics, tricresyl phosphate is widely used as a plasticizer and the flexibility, hardness, water resistance, and inflammability of the plastic can be varied with the amount of plasticizer used. Tricresyl phosphate is used as a solvent for resins and for waterproofing and fireproofing compositions of various types. An "*ortho*-free" grade of tricresyl phosphate is commercially available.

### Toxicity

Experimental work by Smith, Elvove, and Frazier (1) showed that toxicologically, tri-*o*-cresyl phosphate differs from the corresponding cresols, phenols, or their phosphoric acid esters in toxicity and also in manner of action. On subcutaneous or intravenous injections of tri-*o*-cresyl phosphate in the cat or dog, flaccid paralysis of the posterior extremities and to a lesser degree of the anterior, follows after a latent interval varying from 5 to 30 days. The minimum effective dose in the cat is about 0.2 milliliter per kilogram, in the dog about 1 milliliter per kilogram. The curiously delayed action of tri-*o*-cresyl phosphate in the animal body and its highly specific effect on the neuromuscular apparatus is probably due to slow liberation of *o*-cresol in selected areas of the nervous



system after the relatively stable lipoid ester had found its way into the nerve tissues (2). Tri-*o*-cresyl phosphate alone can produce in experimental animals this specific type of paralysis of the extremities. This paralysis is comparable with that which occurred in human victims who drank a fluid extract of Jamaica ginger adulterated with tricresyl phosphate. Several thousand cases occurred in the United States in 1930 and of these ten died. Hunter (3, 4) has shown by means of experiments on domestic fowls that the tri-*o*-cresyl phosphate is toxic while larger doses of tri-*m*-cresyl phosphate produced only weakness of the legs and still larger doses were required for respiratory paralysis. Fowls fed tri-*p*-cresyl phosphate showed no evidence of ill health. Hunter has recorded the toxic effects in three men employed in a plant manufacturing tri-*o*-cresyl phosphate during World War II. The clinical picture is that of a polyneuritis with flaccid paralysis of the distal muscles of the upper and lower extremities. Slow but complete recovery usually occurs. Although there is experimental evidence that tri-*o*-cresyl phosphate can be absorbed through the skin, the port of entry in these cases may have been the respiratory tract. In 1937, an outbreak affected 68 people using salad oil containing 0.4 per cent tri-*o*-cresyl phosphate. Cases also occurred in Germany among factory workers using a fat substitute which contained this substance (Hunter, 3). Hotston (5) has recently reported similar cases in England. Walthard and Walthard (6) reported serious disturbances of the gastrointestinal tract (followed by paralysis of feet, legs, arms, and hands with muscular atrophy) in an epidemic in which 89 cases developed following tri-*o*-cresyl phosphate poisoning.

### Analysis

Tri-*o*-cresyl phosphate existing in the air of work spaces as vapor or present as mist may be quantitatively determined by absorption in a suitable medium and subsequent determination of either the phenol content or the phosphate content of the absorption mixture. In either case, it is necessary to hydrolyze the trapped *o* compound.

The method adopted by Hunter and his associates (3) is the more exact of the two methods for quantitative estimation and is relatively simple. In this method the phosphate portion of the molecule is determined colorimetrically with the usual ammonium molybdate and benzidine reagents.

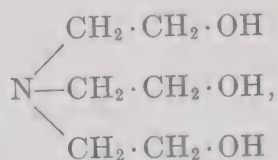
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## TRIETHANOLAMINE

### Characteristics

Triethanolamine,  $\beta, \beta', \beta''$ -trihydroxytriethylamine,



is an organic base related to ammonia in which the three hydrogen atoms have been replaced by the ethanol group ( $\text{HOCH}_2 \cdot \text{CH}_2 -$ ). This substance, which became technically important in 1927, is a colorless liquid soluble in water and intermediate in properties between alcohol and ammonia. Its boiling point is  $227^\circ \text{C}$ . at a pressure of 150 millimeters of mercury. It has a density  $d_{20/20}$  of 1.1258 and its vapor pressure at  $20^\circ \text{C}$ . is less than 0.1 millimeter of mercury. It has a slightly ammoniacal odor, excellent penetrating properties, and is hygroscopic.

Triethanolamine is prepared by allowing ethylene chlorhydrin to react with ammonia. In another special process which is technically important, ammonia reacts with ethylene oxide by opening the oxide ring yielding successively the mono-, di-, and finally triethanolamine.

### Industrial Uses

Triethanolamine combines with free fatty acids to form organic soaps which have solubilities different from those of metallic soaps, particularly in the sense that they are soluble in certain organic solvents, as well as being water soluble. Triethanolamine is a solvent for casein, shellac, dyes, and certain synthetic resins. In the production of urea resins, triethanolamine is particularly useful as a catalyst for the reaction between urea and formaldehyde at a temperature of not over 50° C. This gives a product of extreme clarity in the finished resin. To some extent, triethanolamine is used as a solvent and plasticizer for organic substances, such as nitrocellulose and cellulose acetate. It is used as a penetrating agent in impregnating wood and paper and as a dispersing agent in rubber. Triethanolamine is incorporated into certain therapeutic salves for dermatologic therapy (1).

### Toxicity

The acute and chronic toxic effects of triethanolamine absorption were investigated by Kindsvatter (2). In order to produce acute poisoning, this investigator found that it was necessary to feed relatively large doses, and even so the deaths were caused not by the intrinsic toxicity of the material but rather by its alkalinity. When neutralized, the animals survived and showed no ill effects. The LD<sub>50</sub> dose of triethanolamine was found to be 8 grams per kilogram for both rats and guinea pigs. Mono- and diethanolamine do not enhance the toxicity of triethanolamine. Animals surviving the LD<sub>50</sub> dose followed by a rest period showed no pathology. Absorption through the skin followed the application of large doses. Since ethanolamine has a high boiling point and a low vapor pressure at ordinary temperatures, exposure by inhalation is not a likely

industrial hazard. No maximum allowable concentration value for this substance has been established.

### Analysis

Since atmospheric contamination due to the vapor of triethanolamine is negligible owing to its low volatility, the only likely exposure by inhalation is probably related to mist. The determination of the amount of triethanolamine present in the air may therefore be made by trapping the substance in measured samples of air by bubbling through a fritted glass bubbler containing a measured quantity of standard acid, followed by titration.

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## TRINITROTOLUENE (TNT)

### Characteristics

2,4,6-( $\alpha$ -) Trinitrotoluene,  $\text{CH}_3\text{C}_6\text{H}_3(\text{NO}_2)_3$ , known commercially as TNT, exists as yellow, monoclinic needles which decompose slowly at 150° C. and explode at about 310° C. It melts at 80.9° C., has a specific gravity of 1.654, and is soluble in alcohol and ether. It is insoluble in water. There are several isomeric trinitrotoluenes, namely, 2,3,4-( $\beta$ -), melting point 112° C.; 2,4,5-( $\gamma$ -), melting point 104° C.; 3,4,5-( $\delta$ -), melting point 137.5° C.; 2,3,5-( $\epsilon$ -), melting point 97.2° C.; and 2,3,6-( $\eta$ -), melting point 111° C. The preparation of 2,4,6-( $\alpha$ -) trinitrotoluene is accomplished by nitration of toluene with mixed acid. Commercial  $\alpha$ -TNT is contaminated by small amounts of the isomers  $\beta$  and  $\gamma$  TNT and traces of dinitrotoluene. These by-products depress the melting point of the main product and impart an objectionable greasy character. They are objectionable also because nitro groups in the *o* and *p* position are labile in nature and render the material subject to hydrolysis with liberation of free nitric acid. The reac-



tivity of the undesirable contaminants facilitates their efficient removal. On a technical scale, yields of purified TNT up to 85 per cent are obtained exclusive of any useful by-products. Commercial TNT is handled in blocks. In addition to the explosive character of trinitrotoluene and its ability to form complexes, its methyl group is very reactive to aldehyde reagents. Thus, in the presence of the basic catalyst piperidine and benzaldehyde, these substances when dissolved in alcohol or benzene condense smoothly to form trinitrostilbene.

### Industrial Uses

2,4,6-Trinitrotoluene is a high explosive used in modern ordnance, i.e., as a bursting charge in shells, bombs, and mines. Because it has a marked deficiency in oxygen, it is usually used mixed with substances rich in that element. It is the most widely used shell-firing explosive and is well suited for loading into containers because of its low melting point of 80.9° C. Its importance for military use comes from its comparative excellence in the following respects: its comparative safety in manufacture, transportation, and storage; its nonhygroscopic nature; its stability in contact with metals; and the fact that it is a violent disruptive explosive (1).

### Toxicity

Intensive exposure to trinitrotoluene during wartime (according to Hunter, 2) showed that it could cause dermatitis, cyanosis, gastritis, acute yellow atrophy of the liver, and aplastic anemia. It may enter the body by inhalation of fumes or dust, by ingestion, or by absorption through the skin. The hands and sometimes the face and hair are stained orange in working with TNT. Dermatitis arises on the parts exposed, namely the hands, forearms, legs, wrists, and ankles (3). In these cases, the irritation is so intense that removal from work is essential. The TNT facies is brought about by the combined effects of methemoglobin and vasomotor changes. It is characterized by pallor with a lilac cyanosis of the lips, tongue, lobes of the ears, and curl of the helix of the ear (4). It need not be asso-

ciated with any symptoms, signs of fatigue, or breathlessness and in this way resembles aniline absorption. Webster's test of the urine indicates that TNT is being excreted in altered form without in any way denoting systemic poisoning (5). Breathlessness, constriction felt beneath the sternum, and malaise are suspicious symptoms; gastric ache, anorexia, lassitude, nausea, headache, jaundice, enlarged liver, and an increase in urinary coproporphyrin complete the toxic picture. In all cases the liver, bone marrow, and vascular endothelium are affected simultaneously by TNT although the degree of toxicity is quite variable (6). In some cases, the liver is destroyed and to some extent the marrow, causing an erythroblastic response, yet producing little or no anemia. In these cases, the vascular endothelium is damaged sufficiently to produce a variable number of petechiae. In other cases, the marrow is most heavily affected causing a repression of both the erythropoietic and leukopoietic elements. Toxic jaundice is a rare complication but it has a mortality of 30 per cent, so it must be regarded seriously. Aplastic anemia sometimes occurs but its incidence is very small. Peripheral neuritis rarely results from industrial exposure to TNT (7). Women have been found to be more susceptible to TNT than men, and colored people much less susceptible than white people. Apparently the skin is a significant channel of absorption, although the presence of TNT in the air would necessitate some absorption by respiration. However, von Oettingen and his associates (8) found that TNT is readily absorbed through the respiratory tract when inhaled as dust in addition to absorption through the gastrointestinal tract or the skin. Skin absorption is, however, of minor importance in comparison with the other routes. While a field investigation of 250 men and 103 women in one bomb and shell loading plant during World War II revealed no severe cases of TNT poisoning (9), 22 fatal cases occurring in its manufacture are reported by McConnell and Flinn (10). Hamilton (11) has recently shown that an early reaction to trinitrotoluene poisoning is a rise in the large mononuclear leukocyte

count. The monocyte rise precedes any symptoms of illness and is suggested as useful in the differential diagnosis of trinitrotoluene poisoning. Also the level of hemoglobin and circulating red cells is reduced indicating that TNT acts as an hemolytic agent (12). Prevention of illness due to TNT exposure and contact is best attained by keeping the air free of the compound by means of ventilation and use of respirators, cleanliness of the implements used, and cleanliness of the worker by making use of protective clothing and by particular attention to care of the skin.

### Analysis

The well-known Webster test (5) for the urinary excretion of TNT or its metabolites depends upon the color formed when alcoholic potash is added to an ethereal extract of acidified urine. Methods for the determination of small amounts of trinitrotoluene as an aerial contaminant have been described by Kay (13) (later modified by Cone, 14), by Pinto and Fahy (15), and by Goldman and Rushing (16). A more recent method for the determination of trinitrotoluene has been developed by Cumming and Wright (17), which makes use of portable equipment for the direct determination of TNT in plant atmospheres. Airborne TNT is estimated colorimetrically by absorption of the material from a known volume of air in a mixed solvent of ethyl ketone and cyclohexanone to which a little potassium hydroxide solution has been added. The intense red color is estimated by comparison with standard tintometer discs.

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## TURPENTINE

### Characteristics

Turpentine oil, spirits of turpentine, or turps, is an oil which is obtained by steam distillation of the resinous secretion of the conifers. This secretion consists of a solution of resins in turpentine oil and the residual material from the distillation process in the resin colophony. Considerable variation exists in the constants reported for turpentine oil inasmuch as this substance consists of a mixture of a number of terpenes—pinene, sylvestrene, dipentene, and a host of minor constituents. Essentially it is a colorless,



volatile liquid, having a density varying from 0.856 to 0.87 and a boiling range of 155° to 165° C. Turpentine oil in commerce is characterized by the country of origin, such as American, French, and Greek turpentine oil, with varying constants which reflect slight differences in composition. A so-called "super" turpentine is obtained by rectifying below 160° C. and consists almost entirely of  $\alpha$ -pinene. The persistent smell of turpentine is said to arise from the peroxides formed in it by autoxidation in air. Turpentine oil is almost insoluble in water, but is miscible with absolute alcohol and ether. It dissolves sulfur, phosphorus, and rubber. The chief constituent of turpentine oil is  $\alpha$ -pinene, which occurs naturally in both dextro and laevo forms; that of American or English origin is usually dextrorotatory; and that of French origin is laevorotatory. In the manufacture of wood turpentine and as a result of the destructive distillation of turpentine, a certain amount of dipentene,  $C_{10}H_{16}$ , is produced. Dipentene, which boils at 170° to 178° C. in its technical form, is an excellent solvent for waxes and some bakelites and glyptals and, to some extent, for rubber. While it is a much better solvent than turpentine, the rate of evaporation is somewhat less and it finds its chief application as an anti-skinning agent.

### Industrial Uses

Very large quantities of turpentine are consumed annually in the United States. The apparent United States consumption for the year 1945-46 was 25,620,750 gallons. The turpentine produced in the United States amounts to more than half of the world production. The production of gum distilled turpentine amounted to 12,212,600 gallons whereas that produced from wood distillation amounted to 12,193,950 gallons. The paint and varnish industry is by far the largest user of turpentine. However, a substantial amount is used in shoe polish and leather dressings and in pharmaceuticals and chemicals. Turpentine may be classed as a better solvent than certain petroleum solvents but not so good as the hydrogenated petroleum solvents boiling in the

range of 150° to 200° C. The aromatic solvents are also superior to turpentine. While turpentine is a good solvent for many resins and dissolves most of the varnish resins, fossil resins require heat treatment to render them soluble in turpentine. Turpentine is also a solvent for many of the alkyd resins but some synthetic phenolic resins require cooking in oil before the addition of turpentine. Total production in the United States amounted to 26,892,000 gallons in 1953.

### Toxicity

Turpentine exerts both a systemic and an irritant action. When ingested, turpentine acts as a violent irritant and after absorption, apparently has a specific effect on the kidneys. The symptoms of systemic poisoning in man are nausea and vomiting, colic and diarrhea, painful micturition, hematuria, glycosuria, and coma. The inhalation of turpentine vapor in high concentrations causes rapid breathing, palpitation, vertigo, convulsions, and other nervous disturbances and may be followed by bronchitis and nephritis. Nephritis may also occur as the result of chronic exposure. While turpentine oil is used as a rubefacient, it can cause blisters after long application and the vesication produced is very painful and heals slowly. Danbolt and Burckhardt (1) tested 59 individuals having a positive skin test to turpentine and found that laevo  $\alpha$ -pinene produced a response of the eczematous type, while that due to dextro  $\alpha$ -pinene was of the toxic type. In attempting to explain the beneficial effects of turpentine abscesses in patients with sepsis, Karreth (2) has shown a rapid and large increase in the number of leukocytes and reticulocytes following the intravenous injection of turpentine and considers this an expression of the defense mechanism of the body. No industrial poisoning from dipentene has been reported, although the investigations of Umeda (3) indicate that some toxic effects may result from exposure to dipentene.

Various reports have been made of chronic poisoning due to inhalation of turpentine vapor, but investigation of the blood of workers has revealed no definite blood dyscrasias nor has evidence been found of

chronic damage to mild exposure, including the incidence of Bright's disease among painters. Smyth and Smyth (4), in testing the effect of turpentine on animals at a concentration of 715 parts per million, found no significant blood changes nor any pathology indicating that this concentration was unsafe. Chapman (5) could find no evidence of chronic renal injury in rats exposed to the fumes of turpentine over a long period of time and concludes that neither turpentine nor paint acts as a renal irritant predisposing the human kidney to glomerular nephritis. Nelson and his associates (6) found that 75 parts of turpentine per million of air caused nose and throat irritation in several people and 175 parts per million was intolerable to the majority.

### Analysis

Inasmuch as turpentine, even in the low concentrations present as an aerial contaminant, yields colors with various reagents, a number of procedures of this type may be applied to its detection and estimation, provided suitable air samples can be taken. Turpentine, for instance, produces color reactions with furfural, salicylic aldehyde, and other higher aldehydes in sulfuric acid. When turpentine vapors are absorbed in sulfuric acid and oxidized by chromic acid, the carbon dioxide evolved may be used as a measure of the turpentine present. Estimation may also be made based on the amount of color produced. Turpentine also gives an initial pink color with vanillin in hydrochloric acid which rapidly changes to a blue-green color which is stable after about 30 minutes. By warming, as small a quantity as 0.02 milligram of turpentine may be detected. Snider (7) has found that steam-distilled wood turpentine may be detected when present in gum spirits of turpentine by determining the benzaldehyde present. Benzaldehyde is found only in steam-distilled wood turpentine and not in either gum spirits or sulfate wood turpentine.

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## VINYL CHLORIDE

### Characteristics

Vinyl chloride, chloroethylene,  $\text{CH}_2=\text{CHCl}$ , is a colorless gas which condenses below  $-13.9^\circ\text{C}$ ., freezes at  $-159.7^\circ\text{C}$ ., boils at  $-13.9^\circ\text{C}$ ., has a density  $D_{20/20}$  of 0.9121, and a vapor pressure of 2,300 millimeters of mercury at  $20^\circ\text{C}$ . Its limits of inflammability are 4.0 to 21.7 per cent by volume of air. Vinyl chloride may be prepared by the chlorination of ethylene followed by the elimination of hydrogen chloride. The latter is accomplished industrially by passing the vapor of ethylene dichloride over such contact catalysts as alumina, activated charcoal, or pumice at high temperatures. The process in present use for the technical preparation of vinyl chloride depends upon the direct addition of hydrogen chloride to acetylene in the presence of mercury salts. All compounds containing the vinyl group  $\text{CH}_2=\text{CH}-$  polymerize readily. Vinyl chloride polymerizes on exposure to sunlight and in the presence of peroxides and catalytic substances. The polymers are unusually strong and resistant to water. These polymers are thermoplastic but require the addition of plasticizers in order to speed the softening rate and prevent decomposition. Polymerization, which is activated by the molecular absorption of energy, proceeds rapidly with the formation of chain products which may be interrupted by ring-closure of the two end molecules, by union with the second chain,



or by the addition of a foreign substance. As a consequence a large number of polymers and copolymers having a wide range of physical properties has received industrial attention. The range of the vinyl chloride polymers is increased by copolymerization with vinyl acetate in which the vinyl chloride content varies from 85 to 95 per cent and the molecular weight from 8,500 to 23,000. Polyvinyl chloride forms a series of thermoplastic resins having many of the properties of rubber when modified by various plasticizers. These substances are processed similarly to rubber although they require no vulcanization. The plasticized polyvinyl chloride resins do not deteriorate on contact with air, light, or ozone. They are also moisture resistant and not affected by immersion in strong mineral acids or strong alkalis.

### Industrial Uses

The copolymers of vinyl acetate and vinyl chloride have found extensive use as lithographic varnishes and enamels and coatings for all types of bases, such as cloth, silk, and paper. Polyvinyl chloride has been used as a rubber substitute in many industries, being applied mostly in solution form (1). The plastics igelite and vinylite are polymerization products of vinyl chloride and are used for insulating cables, making X-ray films, and foils. In addition to wire and cable coating material, the polyvinyl resins have received extensive application as liners for tin cans and have practically displaced all other plastics in safety glass for automobiles (2). Vinyl chloride is also used as a refrigerant.

### Toxicity

Patty, Yant, and Waite (3) investigated the physiological properties of vinyl chloride and found that it is less harmful than carbon tetrachloride and chloroform and is similar in action to ethyl chloride. The symptoms produced by inhalation exposure are principally those of narcosis. The respiration varies from an initial rapid, jerky type to a later slow, shallow type. While very high concentrations of 20 to 40 per cent by volume will kill guinea pigs in a short period

of time, 0.5 per cent may be breathed for several hours without acute disturbances of a serious nature. Vinyl chloride does not possess warning properties of the odor or irritation type, but in high concentrations (5 per cent) gives warning by producing symptoms of dizziness and disorientation in advance of any harmful effects.

### Analysis

No method has been developed specifically for the determination of low concentrations of vinyl chloride as an aerial contaminant. The usual procedures for the determination of chlorinated hydrocarbons could be applied, however, in the absence of interfering or complicating substances. Patty and his associates (3) used an explosion pipette (with electrolytic gas to energize the explosion), followed by absorption of the explosion products.

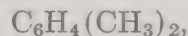
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### XYLENE

#### Characteristics

Xylene, xylol, dimethylbenzene,



is a homologue of benzene. It exists in three forms—the *o*, *m*, and *p*. As used commercially, xylene is a mixture of the three with the *m*-xylene predominant. The first two isomers are colorless liquids, while *p*-xylene is a solid consisting of colorless monoclinic crystals. All are insoluble in water but soluble in alcohol or ether. The highest fraction of "light oil" obtained from the distillation of coal tar contains the xylenes. The following physical characteristics serve to differentiate the isomeric forms of xylene: Boiling point: *o*-, 144.05° C.; *m*-, 139.30° C.; *p*-,

138.40° C. Melting point: *o*-, -25° C.; *m*-, -47.4° C.; *p*-, 13.35° C. Density  $\rho_{20/4}$ : *o*-, 0.88011; *m*-, 0.86407; *p*-, 0.86100. Index of refraction  $n_{20/D}$ : *o*-, 1.50547; *m*-, 1.49749; *p*-, 1.49615. Vapor pressure in millimeters of mercury at 20° C.: *o*-, 10; *m*-, 6.4; *p*-, 16.4. The flash point of commercial xylene is 27° C. With picric acid, xylene forms picrates as follows: *o*-, melting point 88.5° C.; *m*-, melting point 90 to 91.5° C.; *p*-, melting point 90.5° C. *p*-Xylene may be separated from *m*-xylene by high vacuum distillation and in the presence of *o*- and *m*-xylene may be determined by the freezing point method. All three of the xylenes are soluble in methyl nitrite even at -20° C. and in aniline at 20° C. Oxidation with  $\text{KMnO}_4$  in case of *o*-xylene yields phthalic acid, with *m*-xylene, it yields isophthalic acid, and with *p*-xylene, it yields terephthalic acid.

### Industrial Uses

The coke oven production of xylene in the United States during 1944 amounted to 8,669,000 gallons. However, total allocation of xylene for the twelve month period July 1, 1944 to June 30, 1945 amounted to 95,770,000 gallons (1). Production of *p*-xylene in 1954 amounted to 59,188,000 pounds. Important uses for xylene include aviation gasoline blends, protective coatings, medicinals, inks, dyes, intermediates, adhesives and cements, and cleaning fluids.

### Toxicity

The hazards of xylene and toluene include: acute poisoning through breathing the fumes or vapors; chronic poisoning through respiration of small concentrations of the fumes or vapors over a long period of time; dermatitis due to the action of the solvents; and fire and explosion. The data presented in the literature of industrial hygiene with reference to the relative toxicities of benzene, toluene, and the xylenes do not show sufficient clear cut differences to permit any accurate evaluation of their relative toxicities. On the one hand, benzene is generally assumed to have higher toxicity than its methyl homologues (2). However, the inhalation experiments of Lehmann (3) showed xylene to be less toxic than toluene

but both homologues to be more toxic than benzene. Later experiments by other investigators have indicated a different comparative evaluation. In general, the symptoms produced by xylene resemble those of benzene and toluene. There is no marked difference in anesthetic effect but probably a more marked irritant action. While blood damage occurs in chronic or subacute poisoning, the white cells are not greatly decreased. Mild anemia and some enlargement of the liver have been noted with reference to prolonged exposure.

### Analysis

No single method has proved particularly reliable for the detection of xylene and in order to identify the isomeric forms of xylene, extensive chemical examinations, such as nitration, sulfonation, oxidation, or bromination, are necessary with chemical identification of the end products of these reactions. The butanone method described by Yant, Pearce, and Schrenk (4) may be applied to the quantitative estimation of xylene as an aerial contaminant. It may also be estimated by adsorption on air-equilibrated charcoal or on silica gel.

### REFERENCES

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2. Hough, V. H., Gunn, F. D., and Freeman, S.: Studies on the toxicity of commercial benzene and a mixture of benzene, toluene, and xylene. *J. Ind. Hyg. Toxicol.* 26: 296 (1944).
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4. Yant, W. P., Pearce, S. J., and Schrenk, H. H.: A microcolorimetric method for the determination of toluene. U. S. Bur. Mines Repts. Invest. 3323, (1936).

### XYLIDINE

Xylidine, *c,c*-dimethylaniline, aminodimethylbenzene,  $\text{C}_6\text{H}_3(\text{CH}_3)_2\cdot\text{NH}_2$ , exists as six possible isomers, all of which are liquids above 20° C., excepting 3,4-xylidine (3,4-dimethylaniline). The physical properties of these six isomers are briefly summarized in Table 13.

The nitration of crude xylene in industry



yields a mixture of nitroxyls which, when reduced, yields a mixture of a number of xylidines. The chief constituent of the mixture is 2,4-xylidine, which is present to the extent of as much as 60 per cent, and of 2,5-xylidine, which may occur to the extent of 20 per cent. These two components of the mixture are also technically the most important, and they are used in the manufacture of azo dyes. The separation of the various xylidines is effected by crystallization of the hydrochlorides or by taking advantage of the solubility relationships of the sulfonic acid derivatives. These amines are sparingly soluble in alcohol and in ether. With strong mineral acids, as indicated above, they form salts which are more or less soluble in water.

### Industrial Uses

The production of *o*- and *p*-xylidines during 1945 in the United States amounted to 92,000 pounds, while other mixed xylidines were produced to the extent of 378,000 pounds in the same year; in 1954 production was 485,000 pounds. In addition to the use of the xylidines for the manufacture of dye-stuffs, particularly azo dyes, these substances attained some importance in World War II as a possible substitute or in conjunction with tetraethyl lead in blended gasoline.

### Toxicity

The literature concerning the toxicity of xylidine was somewhat meager prior to World War II. According to Flury and Zernik (1), xylidine is qualitatively similar to aniline in its toxic effects. Von Oettingen and his associates (2) found that the vapors of xylidine are about twice as toxic as those of aniline, based on determination of the LD<sub>50</sub> for mice following inhalation. These investigators report that xylidine is a toxic substance which may cause injury to the blood and especially the liver without necessarily causing such alarm signals as the cyanosis, headache, and dizziness which

TABLE 13

Xylidine Isomer		Melt- ing Point °C.	Boil- ing Point °C.	Density	Index of Re- frac- tion
2,3-Xylidine	Liquid		223	0.991	1.570
3,4-Xylidine	Solid	51	226	1.076	
2,4-Xylidine	Liquid		216	0.974	20/4 1.559
2,5-Xylidine	Liquid	15.5	217	0.980 <sup>16°</sup>	
2,6-Xylidine	Liquid		220	0.979	1.561
3,5-Xylidine	Solid		221	0.972	1.558

characterize aniline poisoning. A significant increase of methemoglobin was noted in cats and mice, whereas the methemoglobin level was but slightly affected in other animals. Cutaneous application of xylidine in the case of cats caused progressive depression of the central nervous system, incoordination, loss of appetite, vomiting, and jaundice. While the concentration of xylidine vapor in the air from xylidine-blended gasolines is lower than might be expected and the danger of acute xylidine poisoning from this source appears to be remote, any sludge remaining following the evaporation of gasoline can cause injury. Continued skin contact with xylidine-blended gasoline should be avoided and garments soiled with this material should be discarded. No threshold limit value for xylidine has so far been established.

### Analysis

Xylidine vapor in air may be determined by absorption spectroscopy, by nesslerization, or by diazotization and coupling with H-acid (2). Xylidine present in biological fluids may be separated by steam distillation and subsequently determined by diazotization and coupling with H-acid (2).

### REFERENCES

1. Flury, F., and Zernik, F.: *Schädliche Gase*. J. Springer, Berlin, 1931, p. 442.
2. von Oettingen, W. F., *et al.*: Xylidine (c,c-dimethylaniline): Its toxicity and potential dangers. U. S. Public Health Service, Natl. Insts. Health Bull. No. 188 (1947).

# APPENDIX

## TABLE I

Conversion Table for Gases: Parts per Million Versus Milligrams per Liter<sup>1</sup>

[25° C. and 760 mm. mercury, barometric pressure.]

Molecular Weight	1 Mg./L. p.p.m.	1 p.p.m. Mg./L.	Molecular Weight	1 Mg./L. p.p.m.	1 p.p.m. Mg./L.	Molecular Weight	1 Mg./L. p.p.m.	1 p.p.m. Mg./L.
1.....	24,450	0.0000409	51.....	479	0.002086	101.....	242.1	0.00413
2.....	12,230	.0000818	52.....	470	.002127	102.....	239.7	.00417
3.....	8,150	.0001227	53.....	461	.002168	103.....	237.4	.00421
4.....	6,113	.0001636	54.....	453	.002209	104.....	235.1	.00425
5.....	4,890	.0002045	55.....	445	.002250	105.....	232.9	.00429
6.....	4,075	.0002454	56.....	437	.002290	106.....	230.7	.00434
7.....	3,493	.0002863	57.....	429	.002331	107.....	228.5	.00438
8.....	3,056	.000327	58.....	422	.002372	108.....	226.4	.00442
9.....	2,717	.000368	59.....	414	.002413	109.....	224.3	.00446
10.....	2,445	.000409	60.....	408	.002554	110.....	222.3	.00450
11.....	2,223	.000450	61.....	401	.002495	111.....	220.3	.00454
12.....	2,038	.000491	62.....	394	.00254	112.....	218.3	.00458
13.....	1,881	.000532	63.....	388	.00258	113.....	216.4	.00462
14.....	1,746	.000573	64.....	382	.00262	114.....	214.5	.00466
15.....	1,630	.000614	65.....	376	.00266	115.....	212.6	.00470
16.....	1,528	.000654	66.....	370	.00270	116.....	210.8	.00474
17.....	1,438	.000695	67.....	365	.00274	117.....	209.0	.00479
18.....	1,358	.000736	68.....	360	.00278	118.....	207.2	.00483
19.....	1,287	.000777	69.....	354	.00282	119.....	205.5	.00487
20.....	1,223	.000818	70.....	349	.00286	120.....	203.8	.00491
21.....	1,164	.000859	71.....	344	.00290	121.....	202.1	.00495
22.....	1,111	.000900	72.....	340	.00294	122.....	200.4	.00499
23.....	1,063	.000941	73.....	335	.00299	123.....	198.8	.00503
24.....	1,019	.000982	74.....	330	.00303	124.....	197.2	.00507
25.....	978	.001022	75.....	326	.00307	125.....	195.6	.00511
26.....	940	.001063	76.....	322	.00311	126.....	194.0	.00515
27.....	906	.001104	77.....	318	.00315	127.....	192.5	.00519
28.....	873	.001145	78.....	313	.00319	128.....	191.0	.00524
29.....	843	.001186	79.....	309	.00323	129.....	189.5	.00528
30.....	815	.001227	80.....	306	.00327	130.....	188.1	.00532
31.....	789	.001268	81.....	302	.00331	131.....	186.6	.00536
32.....	764	.001309	82.....	298	.00335	132.....	185.2	.00540
33.....	741	.001350	83.....	295	.00339	133.....	183.8	.00544
34.....	719	.001391	84.....	291	.00344	134.....	182.5	.00548
35.....	699	.001432	85.....	288	.00348	135.....	181.1	.00552
36.....	679	.001472	86.....	284	.00352	136.....	179.8	.00556
37.....	661	.001513	87.....	281	.00356	137.....	178.5	.00560
38.....	643	.001554	88.....	278	.00360	138.....	177.2	.00564
39.....	627	.001595	89.....	275	.00364	139.....	175.9	.00569
40.....	611	.001636	90.....	272	.00368	140.....	174.6	.00573
41.....	596	.001677	91.....	269	.00372	141.....	173.4	.00577
42.....	582	.001718	92.....	266	.00376	142.....	172.2	.00581
43.....	569	.001759	93.....	263	.00380	143.....	171.0	.00585
44.....	556	.001800	94.....	260	.00384	144.....	169.8	.00589
45.....	543	.001840	95.....	257	.00389	145.....	168.6	.00593
46.....	532	.001881	96.....	255	.00393	146.....	167.5	.00597
47.....	520	.001922	97.....	252	.00397	147.....	166.3	.00601
48.....	509	.001963	98.....	249.5	.00401	148.....	165.2	.00605
49.....	499	.002004	99.....	247.0	.00405	149.....	164.1	.00609
50.....	489	.002045	100.....	244.5	.00409	150.....	163.0	.00613

<sup>1</sup> U. S. Bureau of Mines, Technical Paper 248 (1921).



TABLE I

Conversion Table for Gases: Parts per Million Versus Milligrams per Liter<sup>1</sup>—Continued

[25° C. and 760 mm. mercury, barometric pressure.]

Molecular Weight	1 Mg./L. plp.m.	1 p.p.m. Mg./L.	Molecular Weight	1 Mg./L. p.p.m.	1 p.p.m. Mg./L.	Molecular Weight	1 Mg./L. p.p.m.	1 p.p.m. Mg./L.
151.....	161.9	0.00618	201.....	121.6	0.00822	251.....	97.4	0.01027
152.....	160.9	.00622	202.....	121.0	.00826	252.....	97.0	.01031
153.....	159.8	.00626	203.....	120.4	.00830	253.....	96.6	.01035
154.....	158.8	.00630	204.....	119.9	.00834	254.....	96.3	.01039
155.....	157.7	.00634	205.....	119.3	.00838	255.....	95.9	.01043
156.....	156.7	.00638	206.....	118.7	.00843	256.....	95.5	.01047
157.....	155.7	.00642	207.....	118.1	.00847	257.....	95.1	.01051
158.....	154.7	.00646	208.....	117.5	.00851	258.....	94.8	.01055
159.....	153.7	.00650	209.....	117.0	.00855	259.....	94.4	.01059
160.....	152.8	.00654	210.....	116.4	.00859	260.....	94.0	.01063
161.....	151.9	.00658	211.....	115.9	.00863	261.....	93.7	.01067
162.....	150.9	.00663	212.....	115.3	.00867	262.....	93.3	.01072
163.....	150.0	.00667	213.....	114.8	.00871	263.....	93.0	.01076
164.....	149.1	.00671	214.....	114.3	.00875	264.....	92.6	.01080
165.....	148.2	.00675	215.....	113.7	.00879	265.....	92.3	.01084
166.....	147.3	.00679	216.....	113.2	.00883	266.....	91.9	.01088
167.....	146.4	.00683	217.....	112.7	.00888	267.....	91.6	.01092
168.....	145.5	.00687	218.....	112.2	.00892	268.....	91.2	.01096
169.....	144.7	.00691	219.....	111.6	.00896	269.....	90.9	.01100
170.....	143.8	.00695	220.....	111.1	.00900	270.....	90.6	.01104
171.....	143.0	.00699	221.....	110.6	.00904	271.....	90.2	.01108
172.....	142.2	.00703	222.....	110.1	.00908	272.....	89.9	.01112
173.....	141.3	.00708	223.....	109.6	.00912	273.....	89.6	.01117
174.....	140.5	.00712	224.....	109.2	.00916	274.....	89.2	.01121
175.....	139.7	.00716	225.....	108.7	.00920	275.....	88.9	.01125
176.....	138.9	.00720	226.....	108.2	.00924	276.....	88.6	.01129
177.....	138.1	.00724	227.....	107.7	.00928	277.....	88.3	.01133
178.....	137.4	.00728	228.....	107.2	.00933	278.....	87.9	.01137
179.....	136.6	.00732	229.....	106.8	.00937	279.....	87.6	.01141
180.....	135.8	.00736	230.....	106.3	.00941	280.....	87.3	.01145
181.....	135.1	.00740	231.....	105.8	.00945	281.....	87.0	.01149
182.....	134.3	.00744	232.....	105.4	.00949	282.....	86.7	.01153
183.....	133.6	.00748	233.....	104.9	.00953	283.....	86.4	.01157
184.....	132.9	.00753	234.....	104.5	.00957	284.....	86.1	.01162
185.....	132.2	.00757	235.....	104.0	.00961	285.....	85.8	.01166
186.....	131.5	.00761	236.....	103.6	.00965	286.....	85.5	.01170
187.....	130.7	.00765	237.....	103.2	.00969	287.....	85.2	.01174
188.....	130.1	.00769	238.....	102.7	.00973	288.....	84.9	.01178
189.....	129.4	.00773	239.....	102.3	.00978	289.....	84.6	.01182
190.....	128.7	.00777	240.....	101.9	.00982	290.....	84.3	.01186
191.....	128.0	.00781	241.....	101.5	.00986	291.....	84.0	.01190
192.....	127.3	.00785	242.....	101.0	.00990	292.....	83.7	.01194
193.....	126.7	.00789	243.....	100.6	.00994	293.....	83.4	.01198
194.....	126.0	.00793	244.....	100.2	.00998	294.....	83.2	.01202
195.....	125.4	.00798	245.....	99.8	.01002	295.....	82.9	.01207
196.....	124.7	.00802	246.....	99.4	.01006	296.....	82.6	.01211
197.....	124.1	.00806	247.....	99.0	.01010	297.....	82.3	.01215
198.....	123.5	.00810	248.....	98.6	.01014	298.....	82.0	.01219
199.....	122.9	.00814	249.....	98.2	.01018	299.....	81.8	.01223
200.....	122.3	.00818	250.....	97.8	.01022	300.....	81.5	.01227

**Table II**  
**Some End Products of Detoxication of Certain Compounds**  
**of Industrial Interest\***

Substance	Urinary Metabolites	Substance	Urinary Metabolites
Acetaldehyde	Acetic acid	Bromobenzene	Glucuronide 40%; ethereal sulfate 37%; mercapturic acid 21%; bromocatechol 28% of the dose
Acetone	50% or more unchanged in the urine	<i>n</i> -Butanol	1.8% of dose conjugated with glucuronic acid
Acetonitrile	Thiocyanic acid and formic acid	Butan-2-ol	14.4% conjugated with glucuronic acid
Acetophenone	Phenylmethylcarbinol glucuronide 35.7%; hippuric acid 24.3%; mandelic acid and phenylmethylcarbinol (small amounts)	<i>n</i> -Butylbenzene	Phenylacetic acid
<i>n</i> -Amyl alcohol	6.7% conjugated with glucuronic acid	Carbon tetrachloride	51% of absorbed (C <sup>14</sup> ) CCl <sub>4</sub> eliminated by the lung; Remainder mainly in urine and feces
<i>n</i> -Amylbenzene	Benzoic acid	Chlorobenzene	Mainly chlorocatechol conjugated with glucuronic and sulfuric acids; <i>p</i> -chlorophenylglucuronide; <i>p</i> -chloromercapturic acid; 3,4-dihydro-3, 4-dihydroxybenzene
Aniline	<i>p</i> -Acetoamido- and <i>p</i> -amino-glucuronide 10-15%; <i>o</i> - and <i>p</i> -aminophenol as sulfate esters 28%; free aniline 6.5%; a labile glucuronide 50%	<i>o</i> -Chlorophenol	Conjugated with glucuronic and sulfuric acids; chlorocatechol 2.1% of dose
<i>p</i> -Aminophenol	As the <i>o</i> -sulfate ester 20%; A moderate amount of <i>o</i> -glucuronide	<i>o</i> -Cresol	65-72% as glucuronide; 10-15% as ethereal sulfate
Anisole	<i>p</i> -Methoxyphenol conjugated with glucuronic and sulfuric acids; conjugated <i>o</i> -methoxyphenol; unconjugated phenols	Cyclohexane	Adipic acid
Anthracene	1,2-Dihydroxy-1,2-dihydroanthracene and its glucuronide; 1-anthrylmercapturic acid and possibly 9,10-anthraquinone.	DDT	Di-( <i>p</i> -chlorophenyl) acetic acid
Azobenzene	Hydrazobenzene; Aniline free, and probably in conjugation	4,6-Dinitro- <i>o</i> -cresol	6-Acetoamido-4-nitro- <i>o</i> -cresol conjugated 1%; Traces of 4-amino-6-nitro- <i>o</i> -cresol and 3-amino-5-nitrosalicylic acid
Benzaldehyde	Hippuric acid; benzoic acid	Diphenyl	4-Hydroxydiphenyl
Benzene	Phenol 23.5%; quinol 4.8%; catechol 2.2%; hydroquinol 0.3%; phenylmercapturic acid 0.5%; <i>trans-trans</i> -muconic acid 1.3%; eliminated unchanged through the lungs 43%; as CO <sub>2</sub> 1.5%	Diphenyl ether	<i>p</i> -Hydroxyphenyl ether; Small amounts of di-( <i>p</i> -hydroxyphenyl) ether conjugated with sulfuric acid 12%, with glucuronic acid 63%
Benzidine	3-Hydroxybenzidine mainly conjugated with sulfuric acid	Ethanol	Acetaldehyde; acetic acid: CO <sub>2</sub> and H <sub>2</sub> O. 0.5% conjugated with glucuronic acid; not more than 2% eliminated undecomposed
Benzoic acid	Hippuric acid 77%; benzoyl glucuronic acid 11%	Ethylbenzene	Hippuric acid; benzoic acid; methylphenylcarbinol conjugated with glucuronic acid; mandelic acid; 32% of dose conjugated with glucuronic acid
Benzyl alcohol	Hippuric acid 80-90%		
Benzyl chloride	Benzylmercapturic acid		
Benzyl cyanide	Benzoic acid: thiocyanates; phenolic substances		

\* By Dr. Louis J. Sciarini, Yale University Medical School.



Table II—Continued

Substance	Urinary Metabolites	Substance	Urinary Metabolites
Ethylene glycol	Oxalic acid	Phenol	Phenylglucuronide 40–50%; phenylsulfuric acid about 45%; quinol 10%; catechol 0.5–1%
Formaldehyde	Formic acid	Phenylacetic acid	Phenaceturic acid; phenylacetylglucuronide; phenylacetylglutamine
Furfural	Pyromucic acid; Furoylglycine and furoylacryloglycine	Phenylethyl ketone	Benzoic acid
Heptan-4-ol	67.4% conjugated with glucuronic acid	Picric acid	4,6-Dinitro-2-aminophenol and a red pigment
<i>n</i> -Hexadecyl alcohol	Palmitic acid	Propanol	Conjugated with glucuronic acid 0.9%
Hydroxylamine	Traces of nitrite	<i>iso</i> Propyl alcohol	Acetone; conjugated with glucuronic acid 10.2%
Methanol	Formaldehyde; formic acid; CO <sub>2</sub> and H <sub>2</sub> O	<i>n</i> -Propylbenzene	Hippuric acid; conjugated with glucuronic acid 30%; conjugated with sulfuric acid 2%
Methyl chloride	Formic acid	<i>iso</i> Propylbenzene	Conjugated with glucuronic acid 68% and with sulfuric acid 1%
Methyl ethyl ketone	Conjugated with glucuronic acid; 30% excreted unchanged in the urine	Propylene glycol	Propylene glycol glucuronide; lactic acid
Naphthalene	$\alpha$ -Naphthol free and in conjugation with glucuronic and sulfuric acids; naphthalendiols; 1,2-Dihydro-2-hydroxy-1-naphthylglucuronide	Pyridine	Methylpyridium hydroxide conjugated with sulfuric and glucuronic acids
$\alpha$ -Naphthylamine	$\alpha$ -Aminonaphthol conjugated with glucuronic and to a small extent with sulfuric acid	Pyrogallol	Ethereal sulfates; As a monoglucuronide
$\beta$ -Naphthylamine	2-Acetamido-6-hydroxynaphthalene; 2-amido-1-naphthylsulfuric acid; 2-acetyl-amino-6-hydroxynaphthalene; 2-amino-naphthol as ethereal sulfate	Resorcinol	Monoglucuronide 43%; monosulfate 13.5%
Naphthol	2-Naphthylsulfuric acid; 1-Naphthylglucuronide	Thiophene	Probably thioylmercapturic acid
Nicotine	Nicotinic acid	Thiourea	Excreted unchanged
Nitrobenzene	<i>m</i> - and <i>p</i> -Nitrophenol conjugated with glucuronic and sulfuric acids in large amounts; <i>o</i> -Nitrophenol; 4-nitrocatechol; aniline; <i>o</i> -, <i>m</i> - and <i>p</i> -aminophenol	Toluene	Hippuric acid 70–80%
Nitroethane	Acetaldehyde; nitrite; nitrate	<i>p</i> -Toluidine	<i>p</i> -Aminobenzoic acid
<i>o</i> -Nitrophenol	<i>o</i> -Nitrophenol conjugated with glucuronic acid 71% and with sulfuric acid 11%; <i>o</i> -aminophenol 3%	Trichloroethylene	Trichloroethanol glucuronide in large amount; trichloroacetic acid
<i>n</i> -Octyl alcohol	Conjugated with glucuronic acid 9.5%	2,4,6-Trinitrotoluene	2,6-Dinitro-4-hydroxylaminotoluene; 2,6-dinitro-4-aminotoluene; 2,4-dinitro-6-aminotoluene
Pentan-2-ol	Conjugated with glucuronic acid 44.8%	Thymol	Thymolglucuronide; thymol-ethereal sulfate; ethereal sulfate of thymohydroquinone.
Phenanthrene	<i>trans</i> -9,10-dihydroxyphenanthrene; <i>laevo-trans</i> -1,2-dihydroxyphenanthrene	<i>p</i> -Xylene	<i>p</i> -Toluic acid 68%, chiefly as glycine conjugate. Small amounts free or conjugated with glucuronic acid

TABLE III

Threshold Limit Values

Values are given in the following tabulation for the maximum average atmospheric concentration of contaminants to which workers may be exposed for an 8-hour working day without injury to health.

These values are based on the best available information from industrial experience, from experimental studies, and, when possible, from a combination of the two. They are not fixed values, but are reviewed annually by the Committee on Threshold Limits for changes, revisions, or additions as further information becomes available. Threshold Limits should be used as guides in the control of health hazards and should not be regarded as fine lines between safe and dangerous concentrations. They represent only conditions under which it is felt workers may be repeatedly exposed, day after day, without adverse effect on their health. The figures listed refer to average concentrations of an 8-hour working shift rather than a maximum which is not to be exceeded even momentarily. The amount by which these figures may be exceeded for short periods during the working day depends upon a number of factors, such as the nature of the contaminant, whether very high concentrations even for short periods produce acute poisoning, whether the results are cumulative, the frequency with which high values occur and for what periods of time. All must be taken into consideration in arriving at a decision as to whether a hazardous situation is deemed to exist.

These values are not intended for use, or for modification for use, in the evaluation or control of community air pollution or air pollution nuisances.

Threshold Limit Values\*

<i>Gases and Vapors</i>			PPM†
Acetaldehyde.....	200	Butyl acetate ( <i>n</i> -butyl acetate).....	200
Acetic acid.....	10	Butyl alcohol ( <i>n</i> -butanol).....	100
Acetic anhydride.....	5	Butylamine.....	5
Acetone.....	1,000	Butyl cellosolve (2-butoxyethanol)....	200
Acrolein.....	0.5	Carbon dioxide.....	5,000
Acrylonitrile.....	20	Carbon disulfide.....	20
Allyl alcohol.....	5	Carbon monoxide.....	100
Allyl propyl disulfide.....	2	Carbon tetrachloride.....	25
Ammonia.....	100	Cellosolve (2-ethoxyethanol).....	200
Amyl acetate.....	200	Cellosolve acetate (hydroxyethyl ace- tate).....	100
Amyl alcohol ( <i>iso</i> amyl alcohol).....	100	Chlorine.....	1
Aniline.....	5	Chlorine trifluoride.....	0.1
Arsine.....	0.05	Chlorobenzene (monochlorobenzene) ..	75
Benzene (benzol).....	35	Chloroform (trichloromethane).....	100
Benzyl chloride.....	1	1-Chloro-1-nitropropane.....	20
Bromine.....	1	Chloroprene (2-chlorobutadiene).....	25
Butadiene (1,3-butadiene).....	1,000	Cresol (all isomers).....	5
Butanone (methyl ethyl ketone).....	250	Cyclohexane.....	400
		Cyclohexanol.....	100
		Cyclohexanone.....	100
		Cyclohexene.....	400
		Cyclopropane.....	400
		Diacetone alcohol (4-hydroxy-4-meth- ylpentanone-2).....	50
		Diborane.....	0.1
		<i>o</i> -Dichlorobenzene.....	50
		Dichlorodifluoromethane.....	1,000
		1,1-Dichloroethane.....	100

\* Adopted at the Eighteenth Annual Meeting of the American Conference of Governmental Industrial Hygienists, Philadelphia, April, 1956. Reprinted from the A. M. A. Archives of Industrial Health, June 1955, Vol. 11, pp. 521-524. Courtesy of Mr. Allan L. Coleman, Chairman of the Committee on Threshold Limits.

† Parts of vapor or gas per million parts of air, by volume.



	PPM		PPM
1,2-Dichloroethylene.....	200	Methyl chloroform (1,1,1-trichloro-ethane).....	500
Dichloroethyl ether.....	15	Methylcyclohexane.....	500
Dichloromonofluoromethane.....	1,000	Methylcyclohexanol.....	100
1,1-Dichloro-1-nitroethane.....	10	Methylcyclohexanone.....	100
Dichlorotetrafluoroethane.....	1,000	Methyl formate.....	100
Diethylamine.....	25	Methyl isobutyl carbinol (methyl amyl alcohol).....	25
Difluorodibromomethane.....	100	Methylene chloride (dichloromethane).....	500
Diisobutyl ketone.....	50	Naphtha (coal tar).....	200
Dimethylaniline (N-dimethylaniline).....	5	Naphtha (petroleum).....	500
Dimethylsulfate.....	1	Nickel carbonyl.....	0.001
Dioxane (diethylene dioxide).....	100	<i>p</i> -Nitroaniline.....	1
Ethyl acetate.....	400	Nitrobenzene.....	1
Ethyl alcohol (ethanol).....	1,000	Nitroethane.....	100
Ethylamine.....	25	Nitrogen dioxide.....	5
Ethyl benzene.....	200	Nitroglycerin.....	0.5
Ethyl bromide.....	200	Nitromethane.....	100
Ethyl chloride.....	1,000	2-Nitropropane.....	50
Ethyl ether.....	400	Nitrotoluene.....	5
Ethyl formate.....	100	Octane.....	500
Ethyl silicate.....	100	Ozone.....	0.1
Ethylene chlorohydrin.....	5	Pentane.....	1,000
Ethylene diamine.....	10	Pentanone (methyl propyl ketone)....	200
Ethylene dibromide (1,2-dibromo-ethane).....	25	Perchlorethylene (tetrachloroethylene)	200
Ethylene dichloride (1,2-dichloro-ethane).....	100	Phenol.....	5
Ethyleneimine.....	5	Phenylhydrazine.....	5
Ethylene oxide.....	100	Phosgene (carbonyl chloride).....	1
Fluorine.....	0.1	Phosphine.....	0.05
Fluorotrichloromethane.....	1,000	Phosphorus trichloride.....	0.5
Formaldehyde.....	5	Propyl acetate.....	200
Gasoline.....	500	Propyl alcohol ( <i>isopropyl</i> alcohol)....	400
Heptane ( <i>n</i> -heptane).....	500	<i>iso</i> Propylamine.....	5
Hexane ( <i>n</i> -hexane).....	500	Propyl ether ( <i>isopropyl</i> ether).....	500
Hexanone (methyl butyl ketone)....	100	Propylene dichloride (1,2-dichloropropane).....	75
Hexone (methyl isobutyl ketone)....	100	Propylene imine.....	25
Hydrazine.....	1	Pyridine.....	10
Hydrogen bromide.....	5	Quinone.....	0.1
Hydrogen chloride.....	5	Stibine.....	0.1
Hydrogen cyanide.....	10	Stoddard solvent.....	500
Hydrogen fluoride.....	3	Styrene monomer (phenyl ethylene)...	200
Hydrogen peroxide, 90%.....	1	Sulfur dioxide.....	10
Hydrogen selenide.....	0.05	Sulfur hexafluoride.....	1,000
Hydrogen sulfide.....	20	Sulfur monochloride.....	1
Iodine.....	0.1	Sulfur pentafluoride.....	0.025
Isophorone.....	25	<i>p</i> - <i>tert</i> -Butyl toluene.....	10
Mesityl oxide.....	50	1,1,2,2-Tetrachloroethane.....	5
Methyl acetate.....	200	Tetranitromethane.....	1
Methyl acetylene.....	1,000	Toluene (toluol).....	200
Methyl alcohol (methanol).....	200	<i>o</i> -Toluidine.....	5
Methyl bromide.....	20	Trichloroethylene.....	200
Methyl cellosolve (methoxyethanol)...	25	Trifluoromonobromomethane.....	1,000
Methyl cellosolve acetate (ethylene glycol monomethyl ether acetate)...	25	Turpentine.....	100
Methyl chloride.....	100	Vinyl chloride (chloroethylene).....	500
Methylal (dimethoxymethane).....	1,000	Xylene (xylol).....	200

*Toxic Dusts, Fumes and Mists*

	Mg. per Cu. M.
Aldrin (1,2,3,4,10,10-hexachloro-1,4,4a,5,8,8a-hexahydro-1,4,5,8-dimethanonaphthalene).....	0.25
Amate (ammonium sulfamate).....	15
Antimony.....	0.5
Arsenic.....	0.5
Barium (soluble compounds).....	0.5
Cadmium oxide fume.....	0.1
Chlordane (1,2,4,5,6,7,8,8-octachloro-3a,4,7,7a-tetrahydro-4,7-methanoindane).....	2
Chlorinated diphenyl oxide.....	0.5
Chlorodiphenyl (42% chlorine).....	1
Chromic acid and chromates (as CrO <sub>3</sub> ).....	0.1
Crag herbicide (sodium-2,4-dichlorophenoxy ethyl sulfate).....	15
Cyanide (as CN).....	5
2,4-D (2,4-dichlorophenoxyacetic acid).....	10
Dieldrin (1,2,3,4,10,10-hexachloro-6,7-epoxy-1,4,4a,5,6,7,8,8a-octahydro-1,4,5,8-dimethanonaphthalene).....	0.25
Dinitrotoluene.....	1.5
Dinitro- <i>o</i> -cresol.....	0.2
EPN (ethyl- <i>p</i> -nitrophenyl thionobenzenephosphonate).....	0.5
Ferrovandium dust.....	1
Fluoride.....	2.5
Hydroquinone.....	2
Iron oxide fume.....	15
Lead.....	0.15
Lindane (hexachlorocyclohexane, gamma isomer).....	0.5
Magnesium oxide fume.....	15
Malathion (O,O-dimethyl dithiophosphate of diethyl mercaptosuccinate).....	15
Manganese.....	6
Mercury.....	0.1
Mercury (organic compounds).....	0.01
Methoxychlor (2,2-diparamethoxyphenyl-1,1,1-trichloroethane).....	15
Molybdenum	
Soluble compounds.....	5
Insoluble compounds.....	15
Parathion (O,O-diethyl-O- <i>p</i> -nitrophenyl thiophosphate).....	0.1
Pentachloronaphthalene.....	0.5
Pentachlorophenol.....	0.5

Mg. per Cu. M.

Phosphorus (yellow).....	0.1
Phosphorus pentachloride.....	1
Phosphorus pentasulfide.....	1
Picric acid.....	0.1
Selenium compounds (as Se).....	0.1
Sodium hydroxide.....	2
Sulfuric acid.....	1
TEDP (tetraethyl dithionopyrophosphate).....	0.2
TEPP (tetraethyl pyrophosphate).....	0.05
Tellurium.....	0.1
Tetryl (2,4,6-trinitrophenylmethylnitramine).....	1.5
Titanium dioxide.....	15
Trichloronaphthalene.....	5
Trinitrotoluene.....	1.5
Uranium	
Soluble compounds.....	0.05
Insoluble compounds.....	0.25
Vanadium	
V <sub>2</sub> O <sub>5</sub> dust.....	0.5
V <sub>2</sub> O <sub>5</sub> fume.....	0.1
Zinc oxide fume.....	15
Zirconium compounds (as Zr).....	5

*Mineral Dusts*

	MPPCF†
Aluminum oxide.....	50
Asbestos.....	5
Dust (nuisance, no free silica).....	50
Mica (below 5% free silica).....	20
Portland cement.....	50
Talc.....	20
Silica	
High (above 50% free SiO <sub>2</sub> ).....	5
Medium (5 to 50% free SiO <sub>2</sub> ).....	20
Low (below 5% free SiO <sub>2</sub> ).....	50
Silicon carbide.....	50
Slate (below 5% free SiO <sub>2</sub> ).....	50
Soapstone (below 5% free SiO <sub>2</sub> ).....	20
Total dust (below 5% free SiO <sub>2</sub> ).....	50

Radioactivity: For permissible concentrations of radioisotopes in air, see "Maximum Permissible Amounts of Radioisotopes in the Human Body and Maximum Permissible Concentrations in Air and Water", Handbook 52, National Bureau of Standards (1953); also Handbook 59 (1954).

† Millions of particles per cubic foot of air.



TABLE IV

Comparative Toxicities of Various Substances Based upon the LD<sub>50</sub> Value  
for Oral Administration to Rats

Substance	Mgs./Kg.	Toxicity*	Substance	Mgs./Kg.	Toxicity*
Acetic acid	3310	IV	2,4-Dinitrophenol	30	I
Acetic anhydride	1780	IV	1,4-Dioxane	5325	IV
Acetanilide	800	III	Ethanol	13600	IV
Acetone	9750	IV	Ethylacrylate	1020	IV
Acetonitrile	3800	IV	Ethylamine	400	III
Acetosalicyclic acid	1360	IV	Ethylenediamine	1160	IV
Acridine	2140	IV	Ethylene glycol	6122	IV
Acrolein	46	I	Formaldéhyde	800	III
Acrylonitrile	93	II	Furfuryl alcohol	275	III
Aldrin	67	II	Hexanal	4520	IV
Allyl alcohol	64	II	1-Hexanol	4870	IV
<i>m</i> -Aminophenol	1000	IV	2-Hexanone	2590	IV
Aminothiazole	480	III	Hexylamine	670	III
Ammonium sulfamate	3900	IV	Hydroquinone	320	III
<i>tert</i> -Amyl alcohol	1000	IV	Hydroxyethyleneimine	74	II
Aniline	460	III	<i>iso</i> Bornylthiocyanate	1000	IV
Antabuse	8600	IV	<i>iso</i> Propyl alcohol	5840	IV
Arsenic trioxide	138	II	Lead arsenate	825	III
Benzene hexachloride	125	II	Malathion	1400	IV
Benzoic acid	1714	IV	Mercuric chloride	37	I
Benzyl alcohol	3100	IV	Methoxychlor	6000	IV
Biphenyl	3280	IV	Methyl carbitol	9210	IV
Boric acid	2660	IV	Methyl iodide	150	II
Butyl acrylate	3730	IV	Methylmethacrylate	9360	IV
<i>n</i> -Butyl alcohol	4360	IV	Morpholine	1600	IV
<i>n</i> -Butylamine	500	III	$\alpha$ -Naphthylthiourea	6.9	I
Butyl ether	7400	IV	Nicotine	50	I
<i>p</i> - <i>tert</i> -Butyltoluene	1543	IV	Parathion	6	I
Butyric acid	2940	IV	Pentachlorophenol	125	II
Carbitol	6500	IV	Phenol	530	III
Chloroacetamide	3100	IV	Phenothiazine	5000	IV
Chloral hydrate	800	III	<i>o</i> -Phenylphenol	2700	IV
Chlordane	470	III	Phenylthiourea	20	I
Chloroacetic acid, mono-	76	II	<i>o</i> -Phthalic acid	7500	IV
Chloroacetic acid, tri-	3320	IV	Piperonyl butoxide	11500	IV
1-Chloronitropropane	50	I	Propanol-1	1870	IV
<i>p</i> -Cresol	1800	IV	Propionaldehyde	1410	IV
Crotonaldehyde	300	III	Pyrethrins	1500	IV
2,4-D	666	III	Pyridine	1580	IV
DDD	3400	IV	Pyrolan	90	II
DDT	420	III	Quinoline	460	III
Dehydroacetic acid	570	III	Rotenone	132	II
Dicumarol	541	III	Salicylamide	1400	IV
Dieldrin	87	II	Sodium azide	46	I
Dimetan	150	II	Sodium fluoride	200	II
Diethylamine	540	III	Sodium fluoroacetate	2.5	I
Diethyl sulfate	880	III	Strychnine	16.2	I
Dimethyl phthalate	8200	IV	Tetraethylpyrophosphate	2	I
Dimethyl sulfate	440	III	Thiourea	1830	IV
4,6-Dinitrobutylphenol	60	II	Toxaphene	69	II
4,6-Dinitro- <i>o</i> -cresol	30	I	Triethylamine	460	III
4,6-Dinitrocyclohexyl-phenol	180	II	Thallium sulfate	15	I

\* I, extremely toxic; II, very toxic; III, moderately to toxic; IV, slightly to nearly nontoxic.





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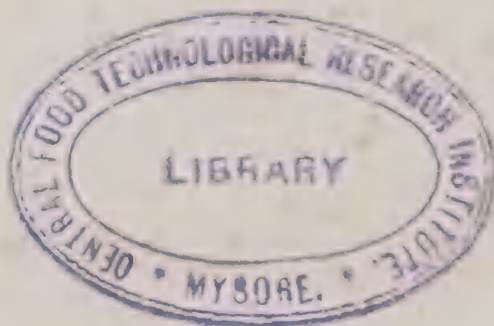
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